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(54) **OCULAR IMPLANT WITH THERAPEUTIC AGENTS AND METHODS THEREOF**

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See application file for complete search history.

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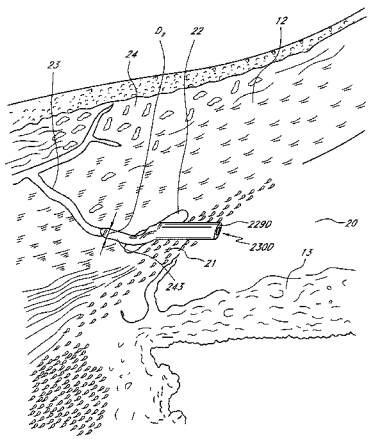
(57) **ABSTRACT**

Implants and methods for treating ocular disorders are provided. One method involves introducing an implant into an anterior chamber of an eye. The implant is implanted into eye tissue adjacent the anterior chamber such that a proximal end of the implant resides in the anterior chamber following implantation. A therapeutic agent is eluted from the implant into the eye. Desirably, the release of the therapeutic agent from the implant is controlled. The controlled release of the therapeutic agent can be at a chosen rate and/or for a selected duration which can be episodic or periodic. The therapeutic agent can be an antiproliferative agent, an anti-inflammatory drug, or a compound for treating glaucoma or ocular hypertension.

17 Claims, 56 Drawing Sheets



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continuation-in-part of application No. 10/395,633, filed on Mar. 21, 2003, now abandoned, which is a continuation of application No. 09/549,350, filed on Apr. 14, 2000, now Pat. No. 6,638,239, said application No. 10/706,300 is a continuation-in-part of application No. 10/634,213, filed on Aug. 5, 2003, now Pat. No. 7,867,186, which is a continuation-in-part of application No. 10/118,578, filed on Apr. 8, 2002, now Pat. No. 7,135,009, said application No. 10/706,300 is a continuation-in-part of application No. 10/046,137, filed on Nov. 8, 2001, now abandoned.

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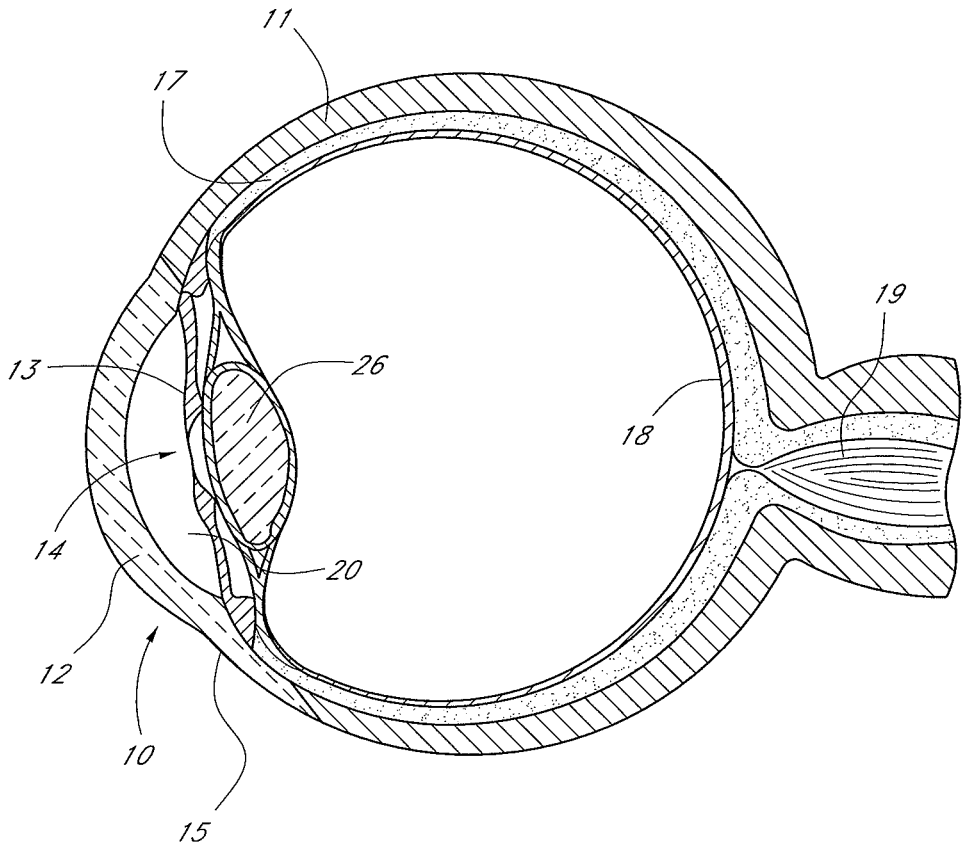

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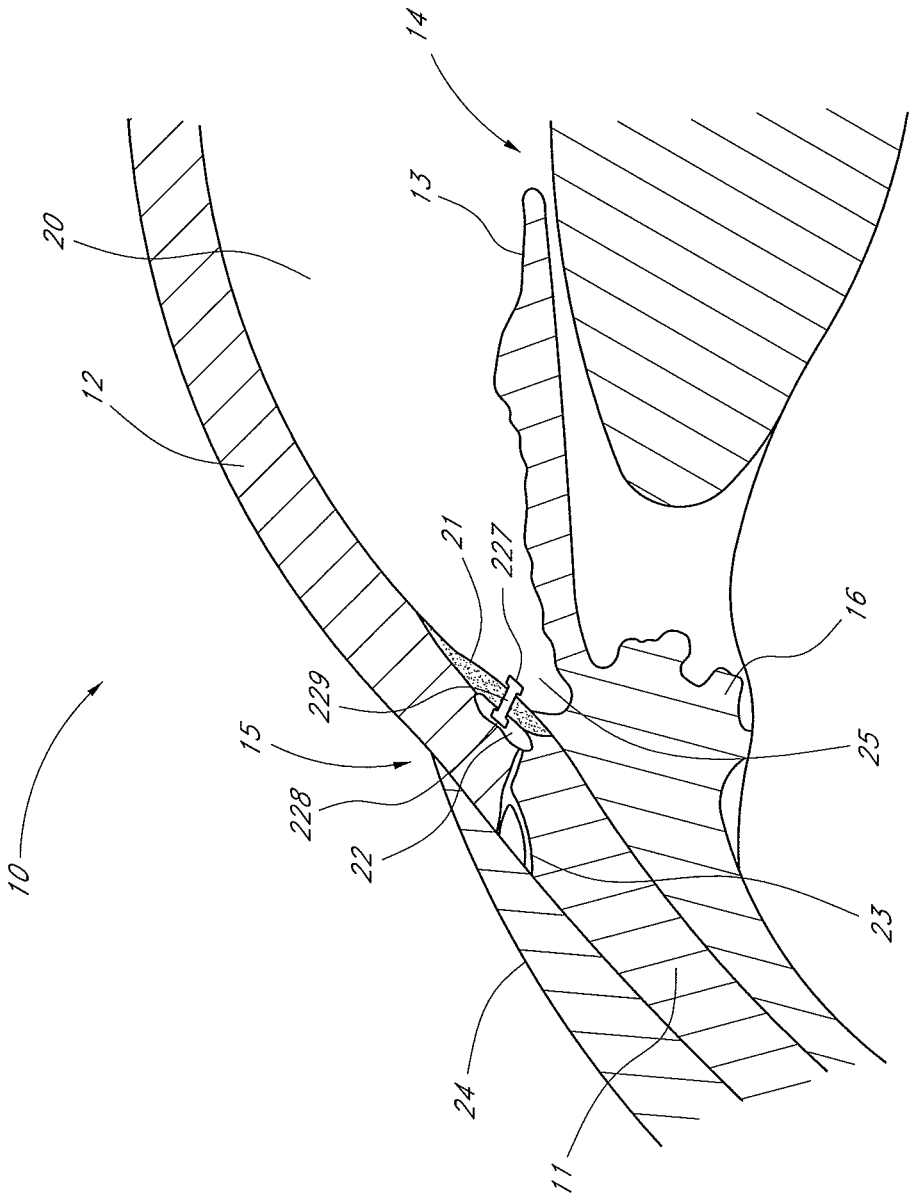

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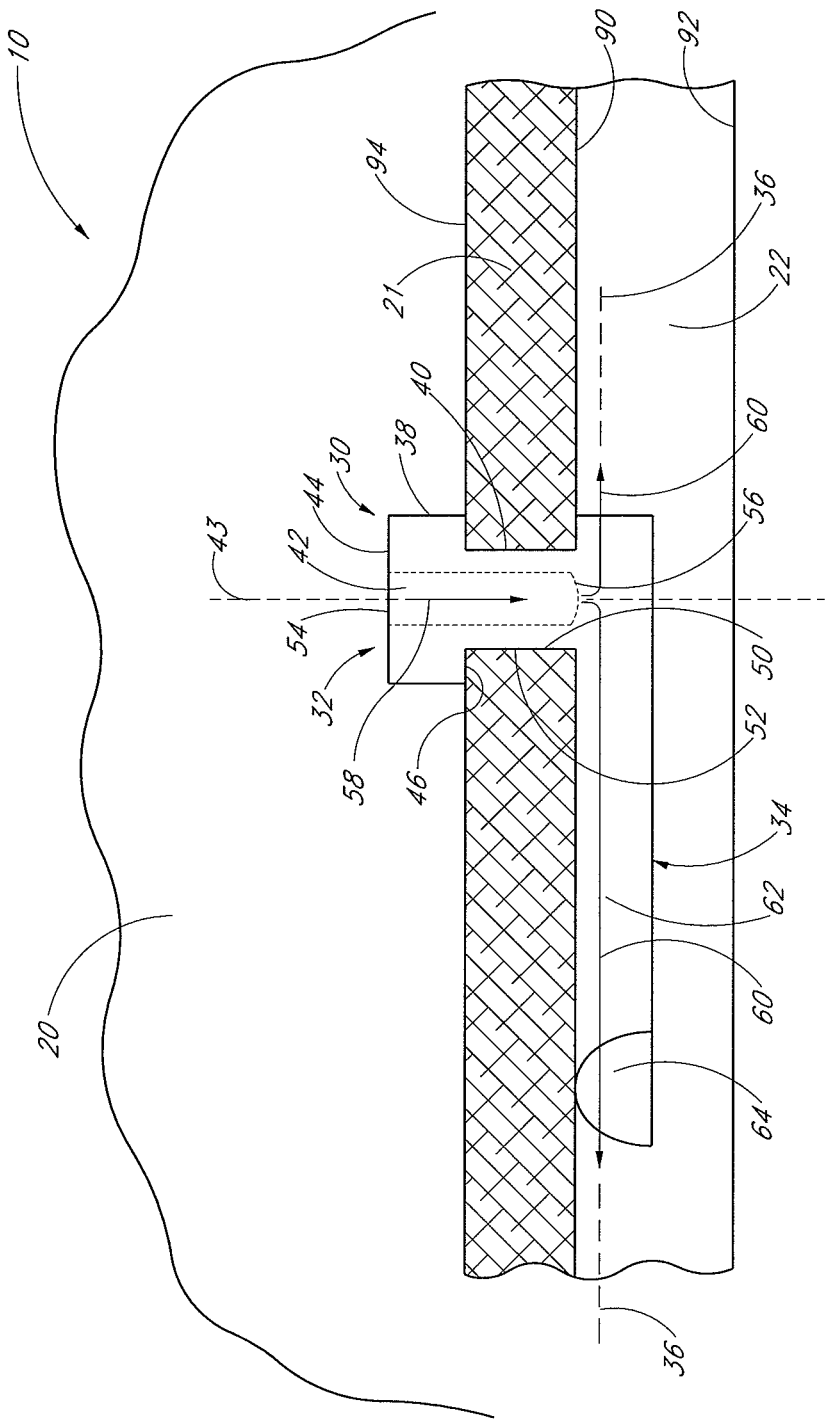
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FIG. 3

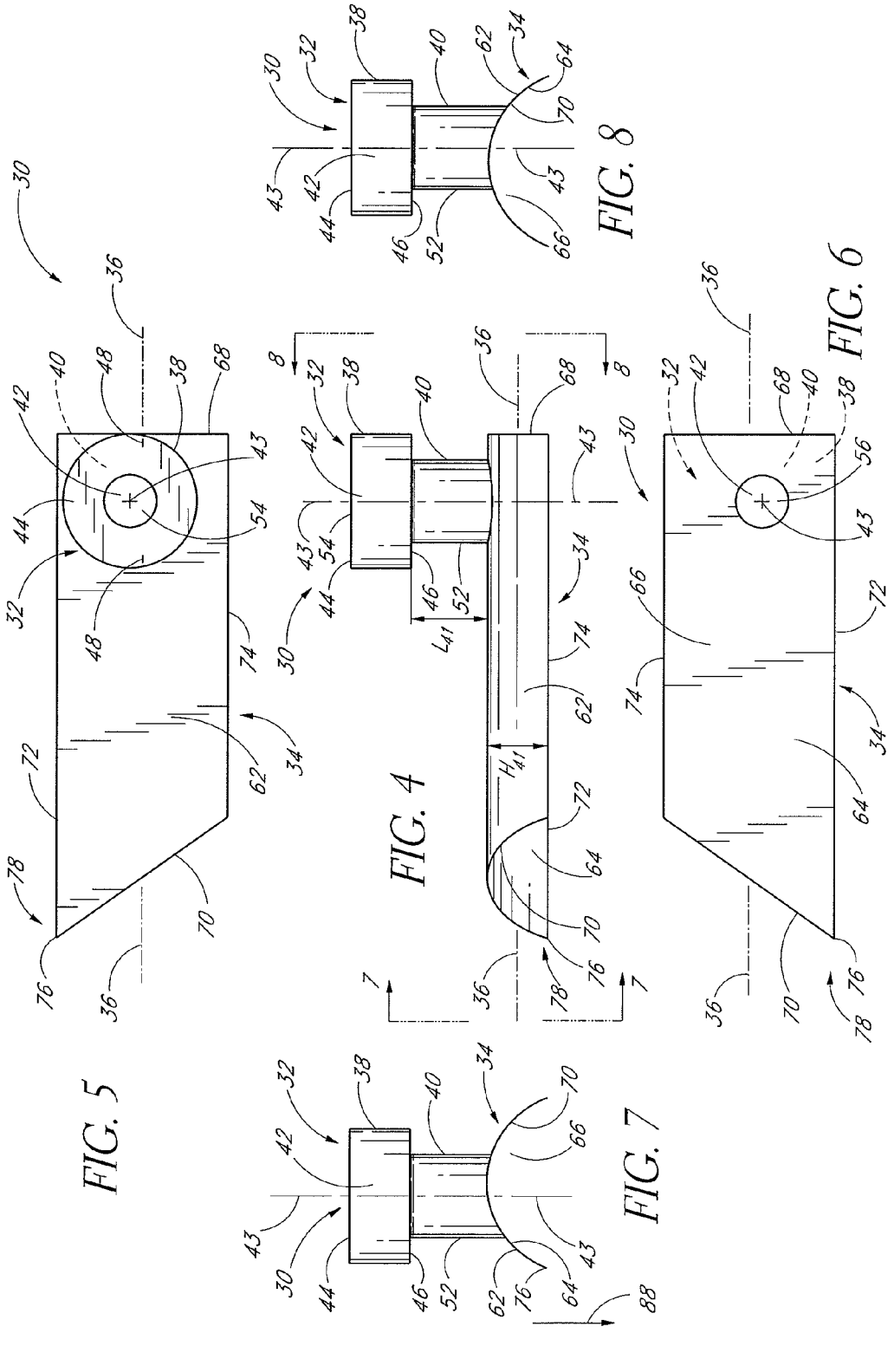
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FIG. 6
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FIG. 7

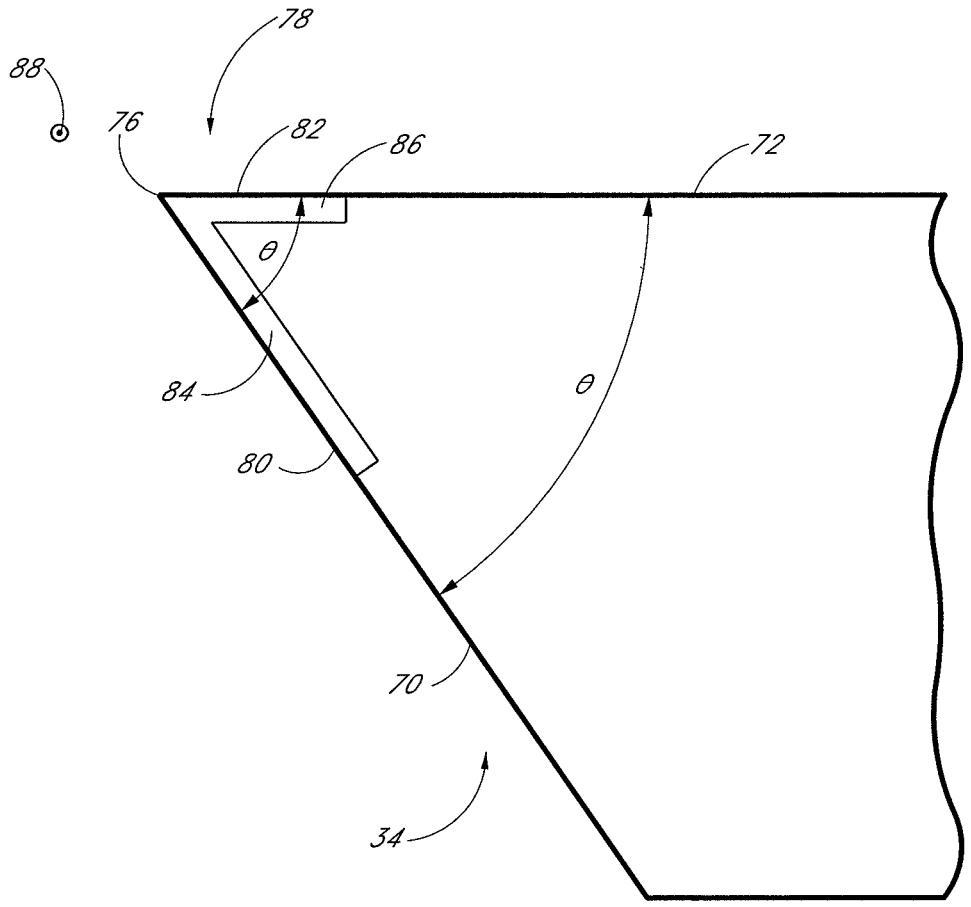
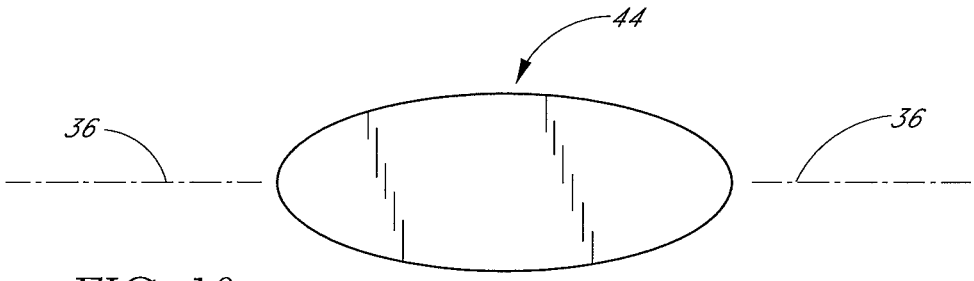


FIG. 9



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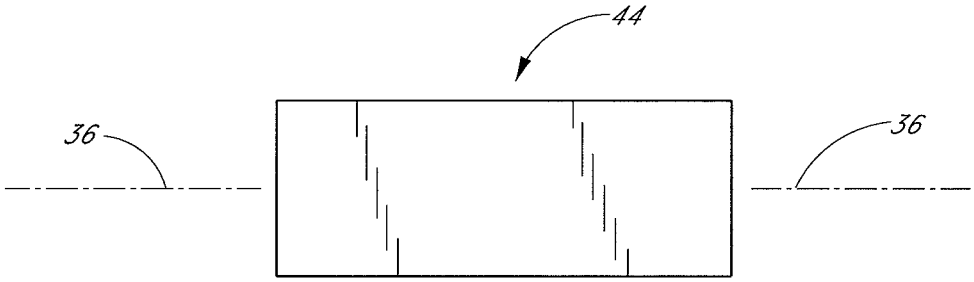

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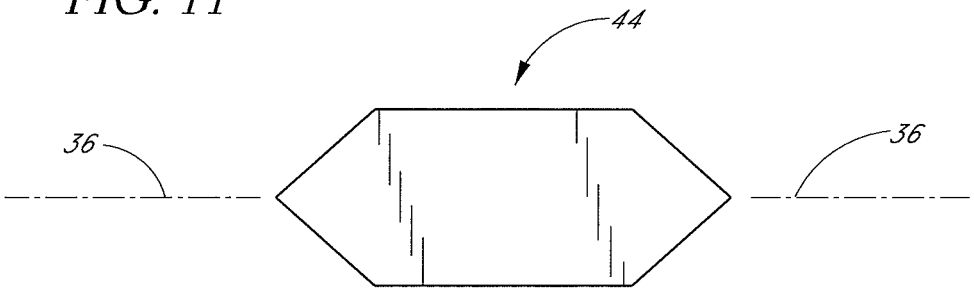

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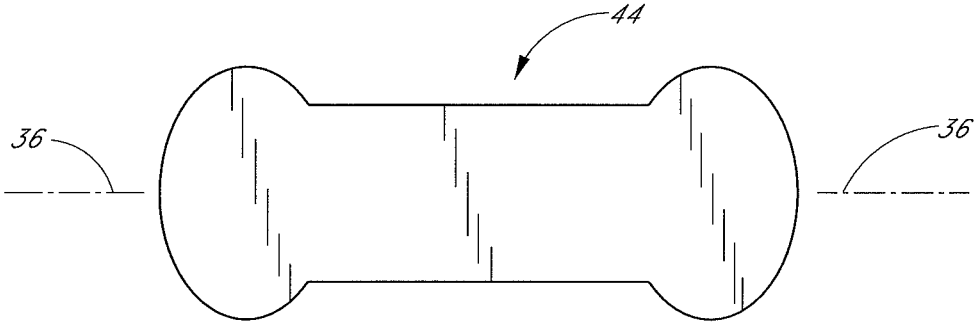

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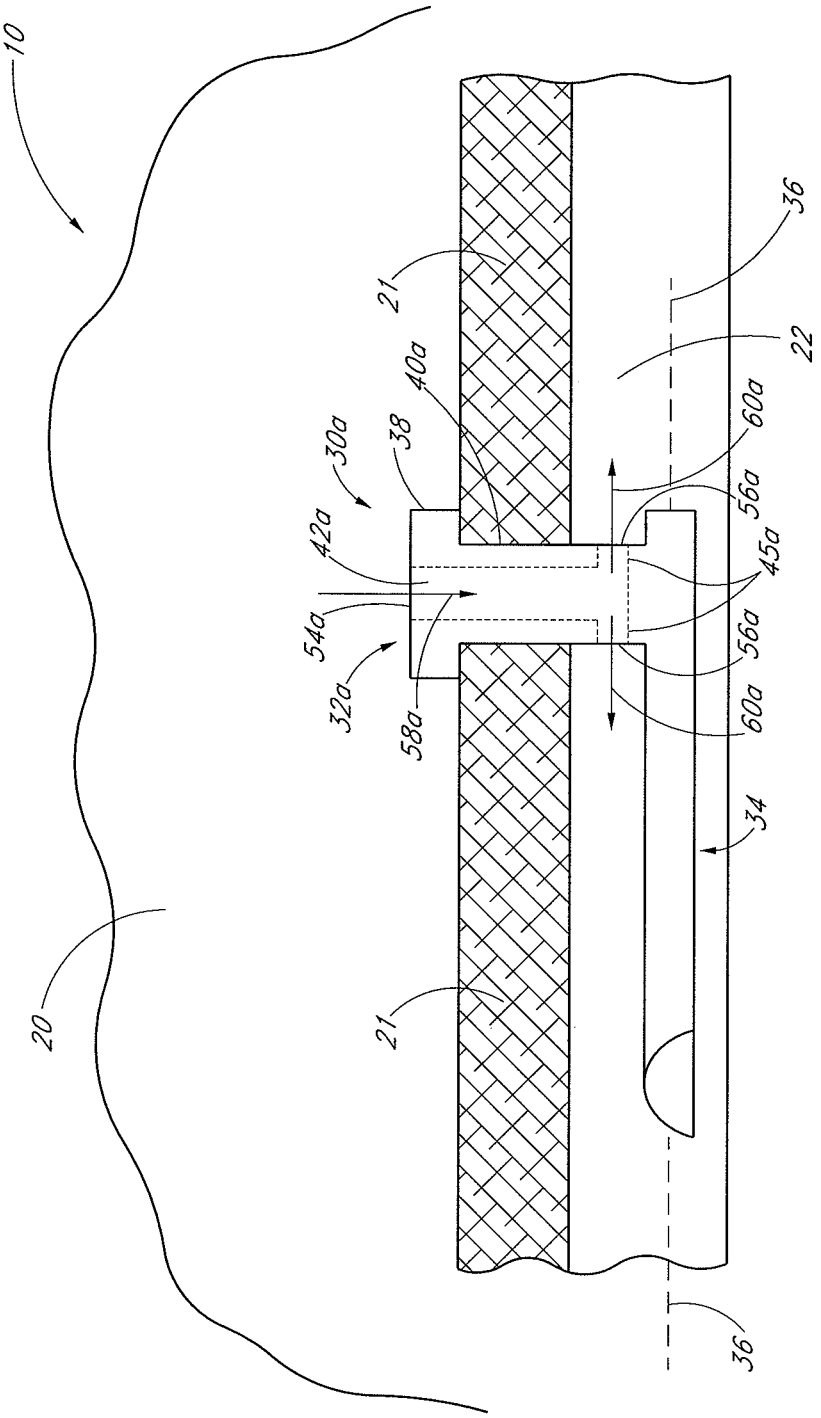
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FIG. 14

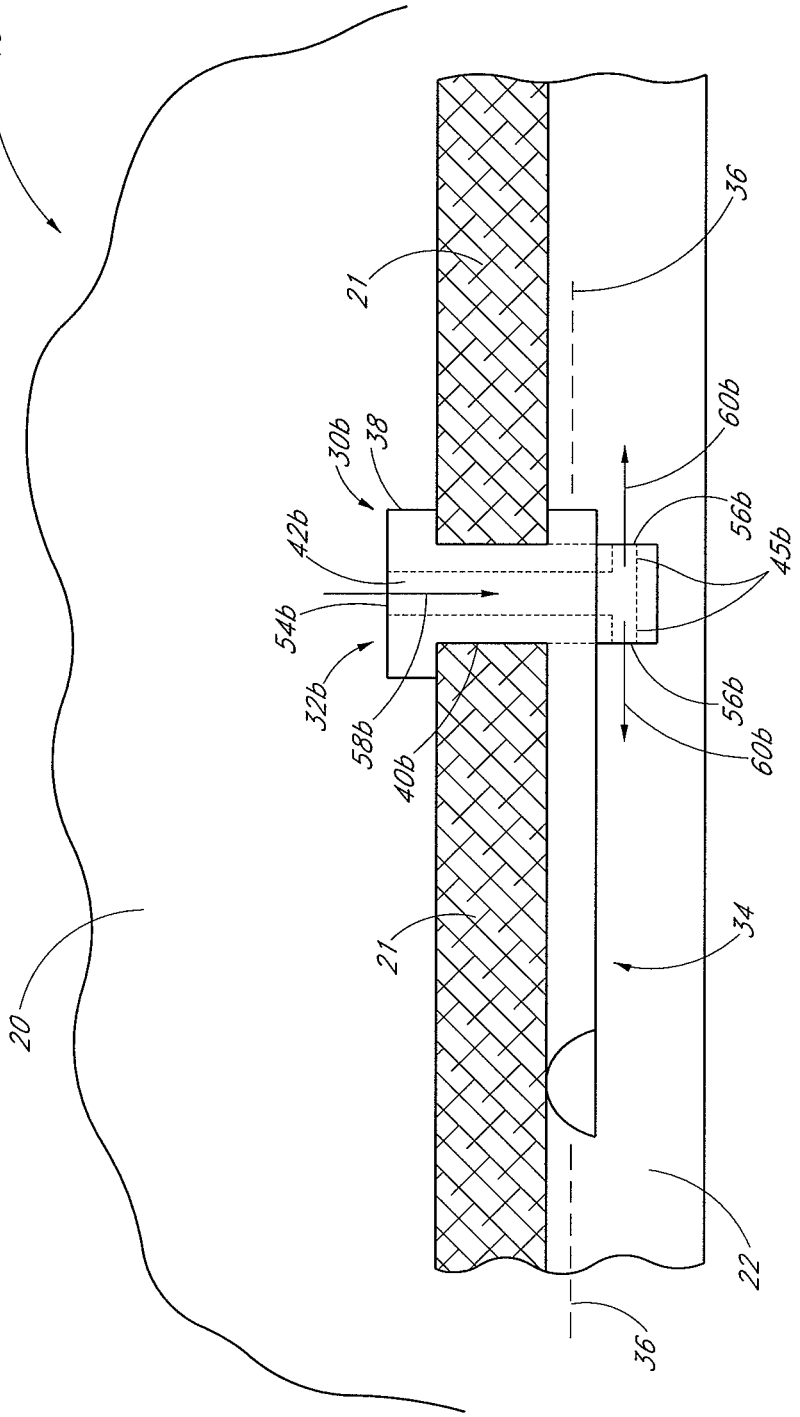
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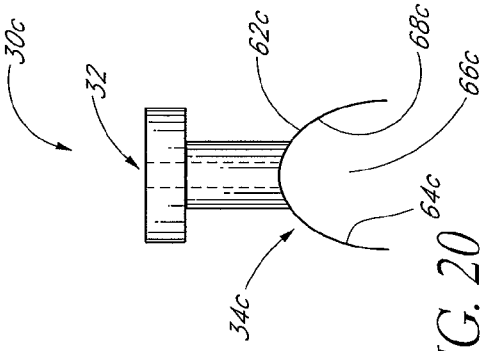
FIG. 15



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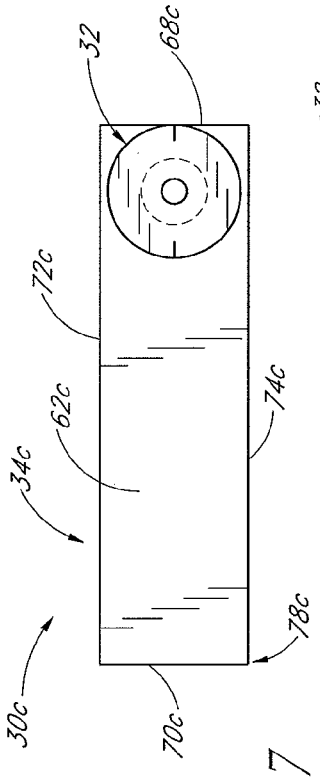
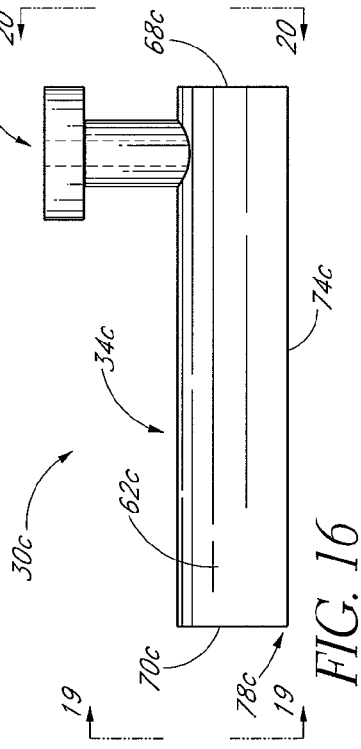


FIG. 17



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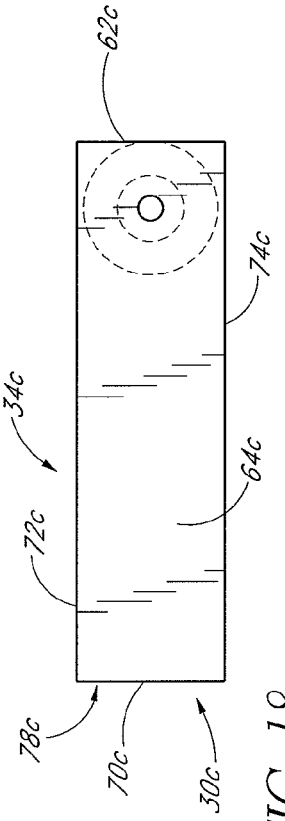

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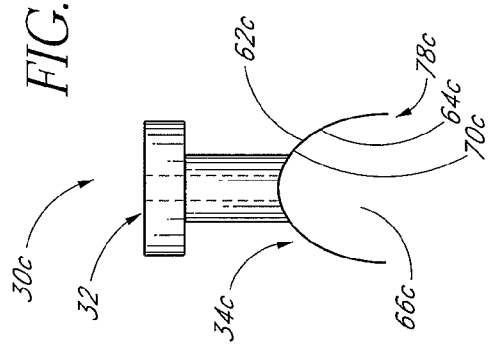

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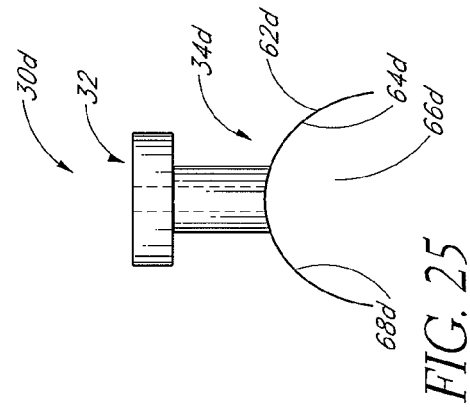

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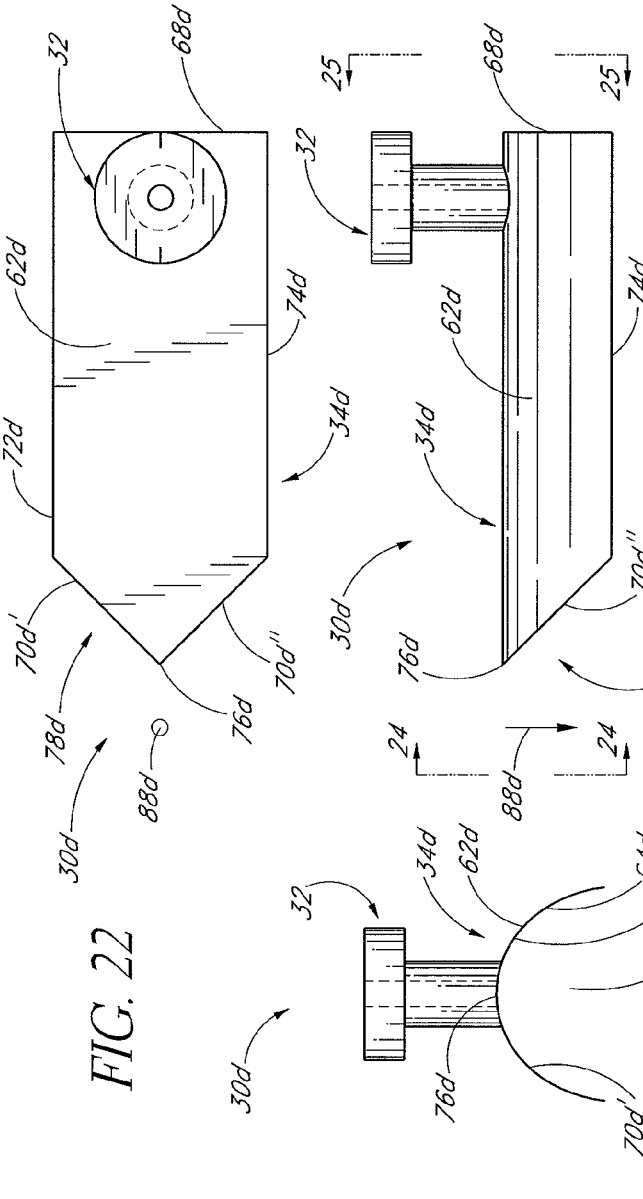

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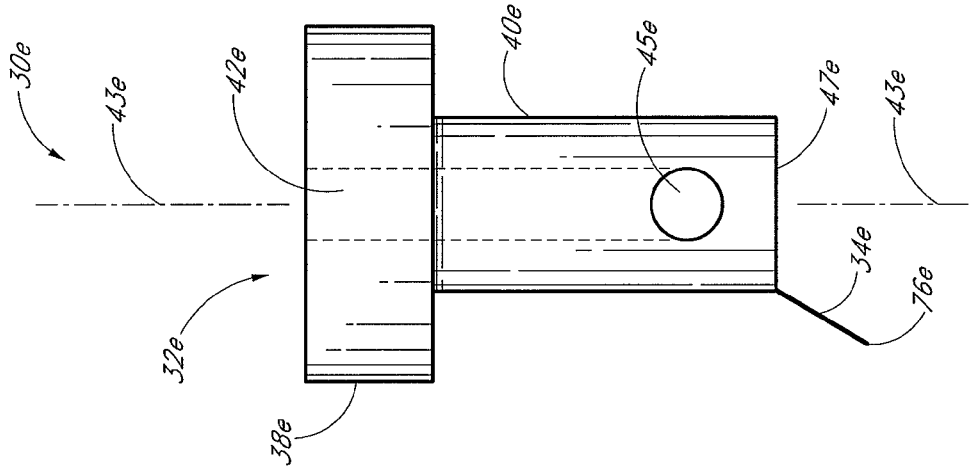
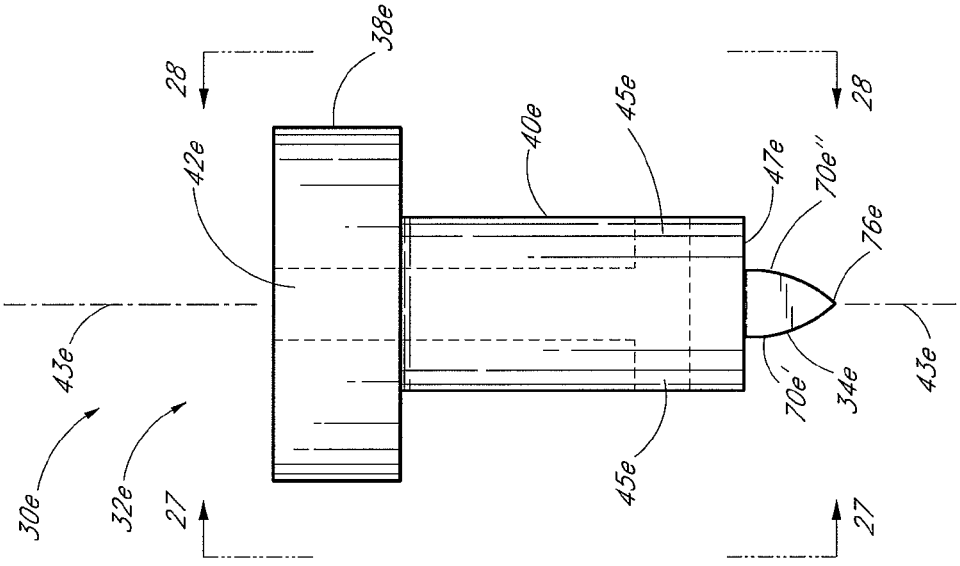


FIG. 28



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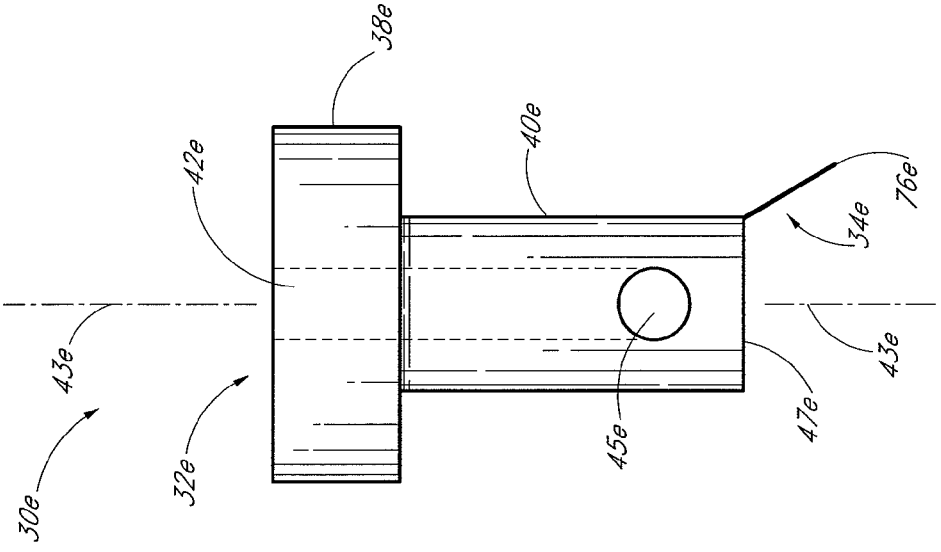
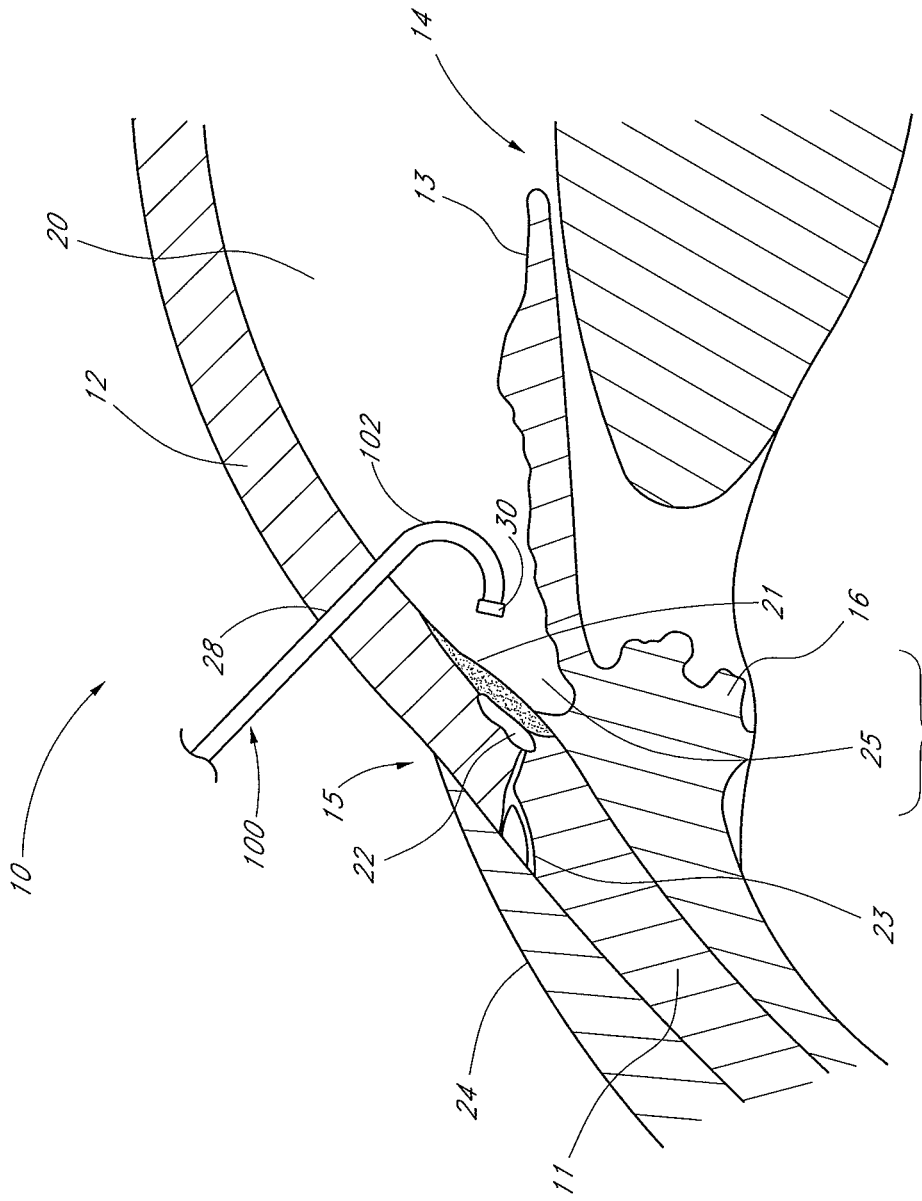


FIG. 27



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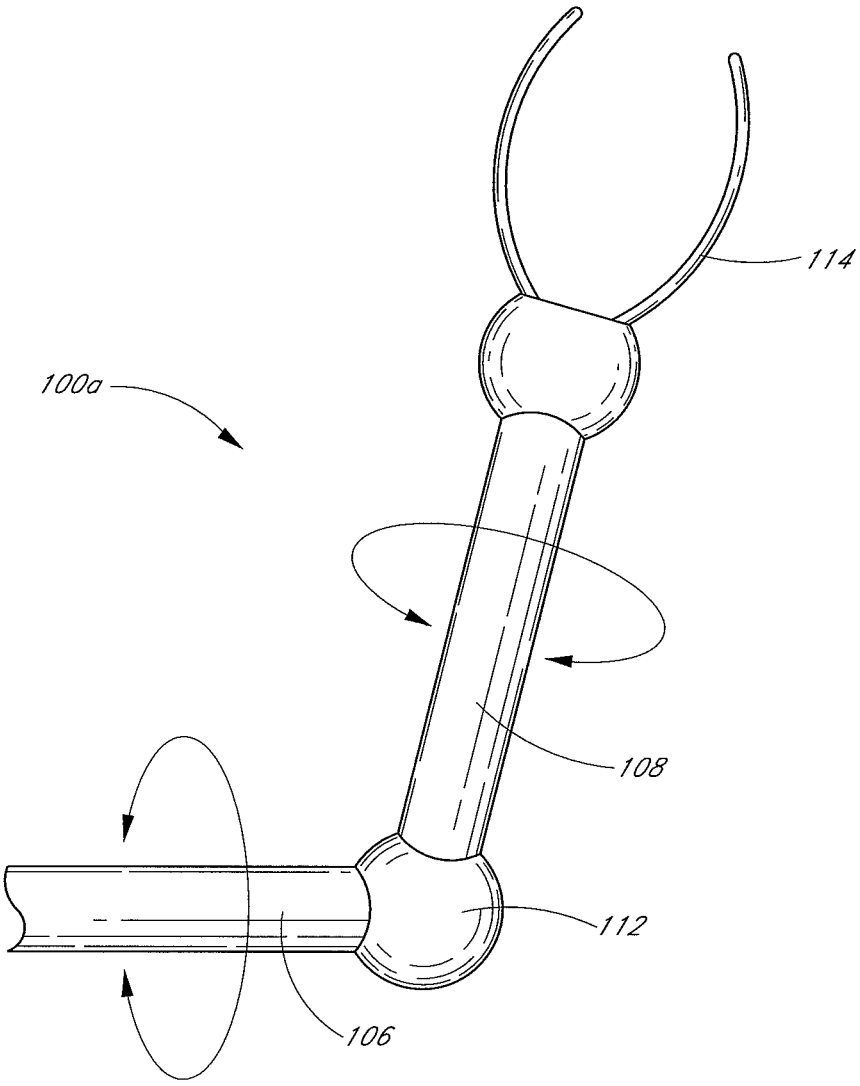

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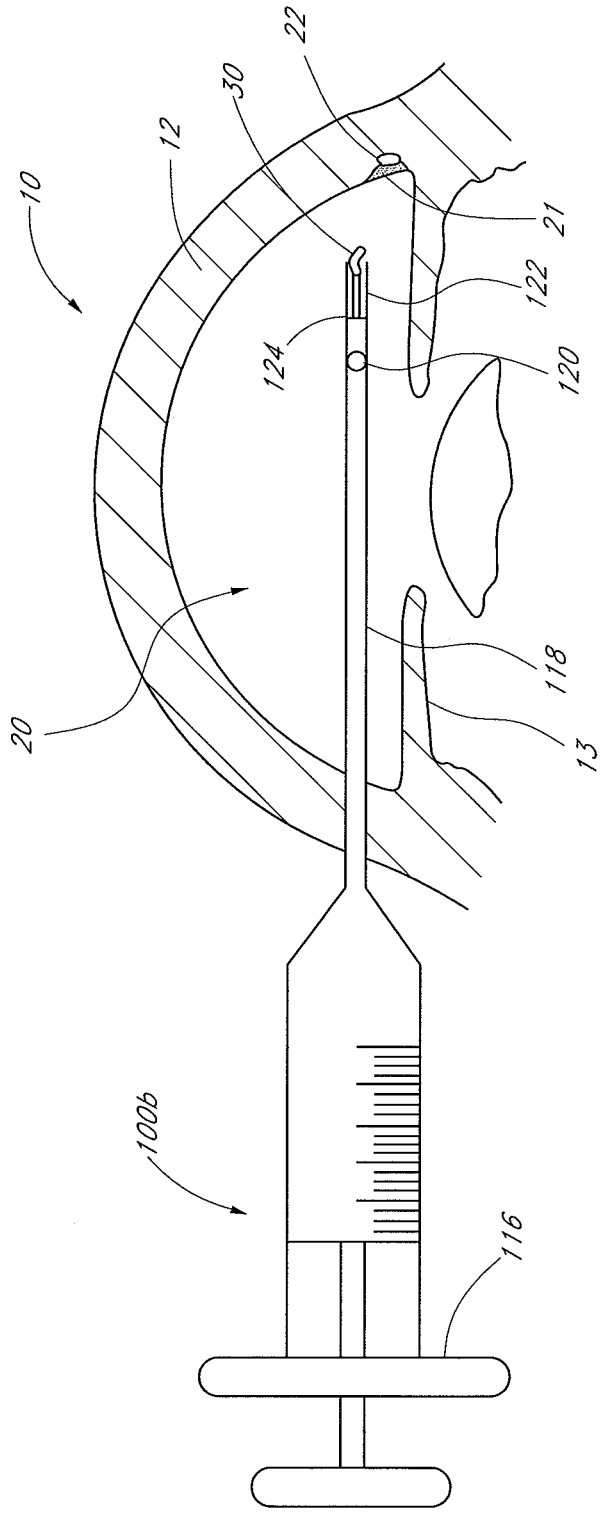

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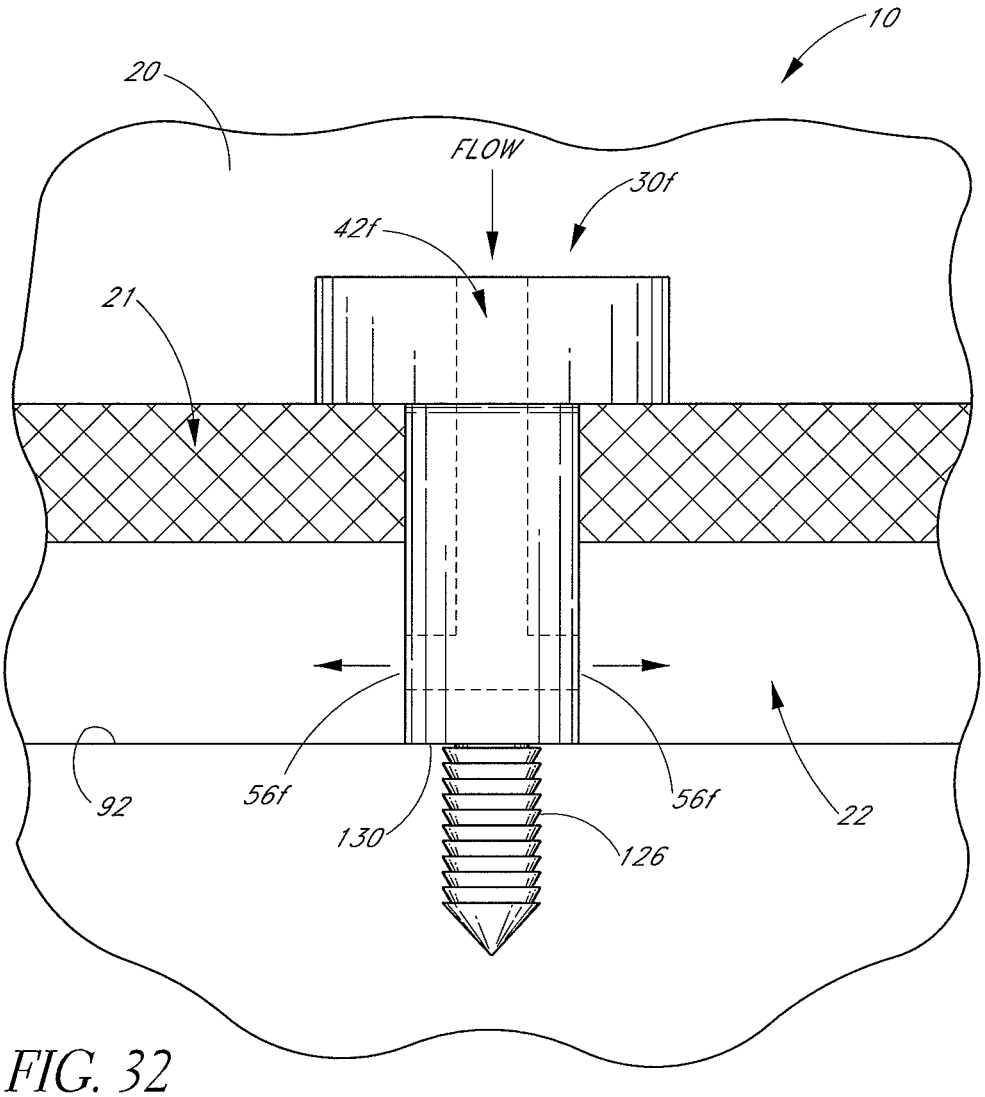

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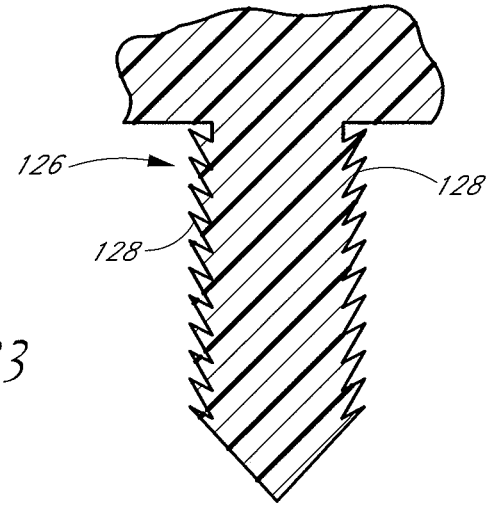

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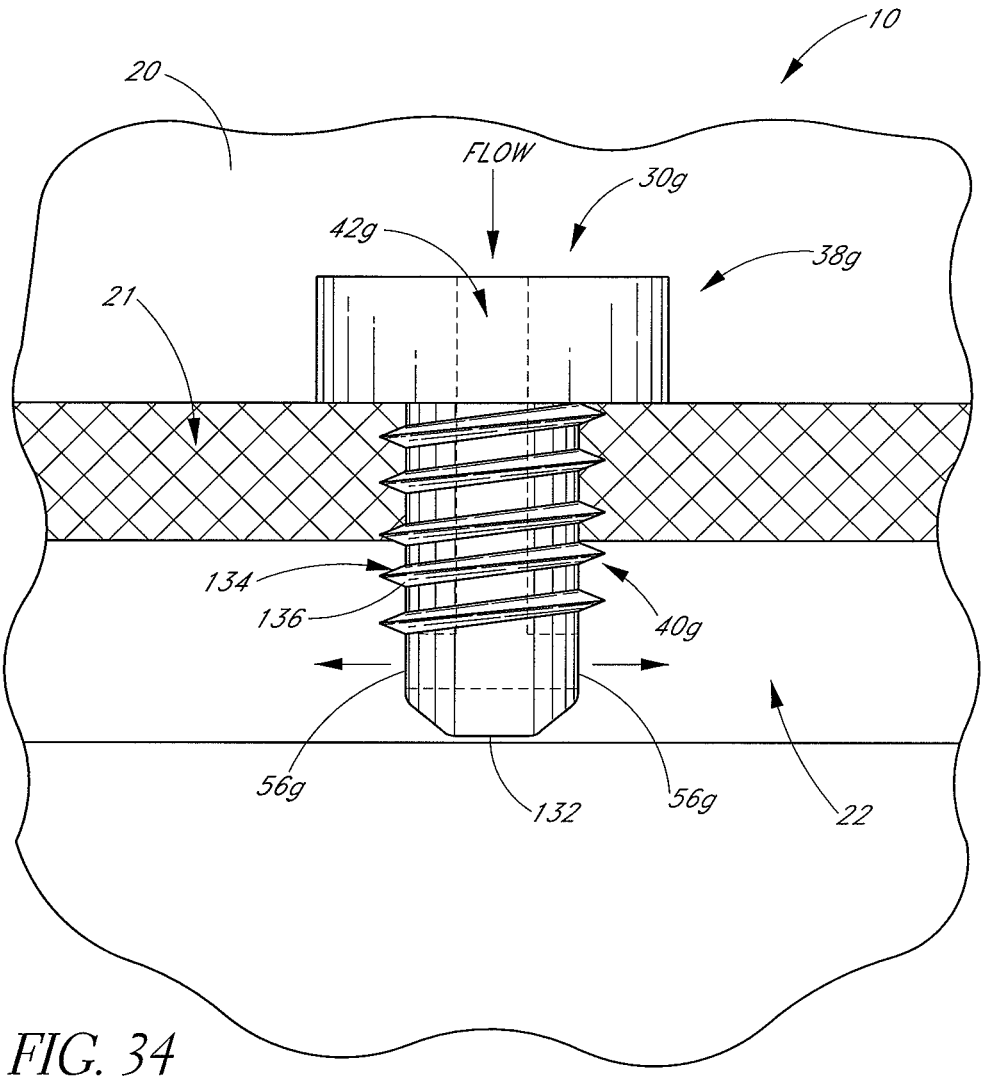

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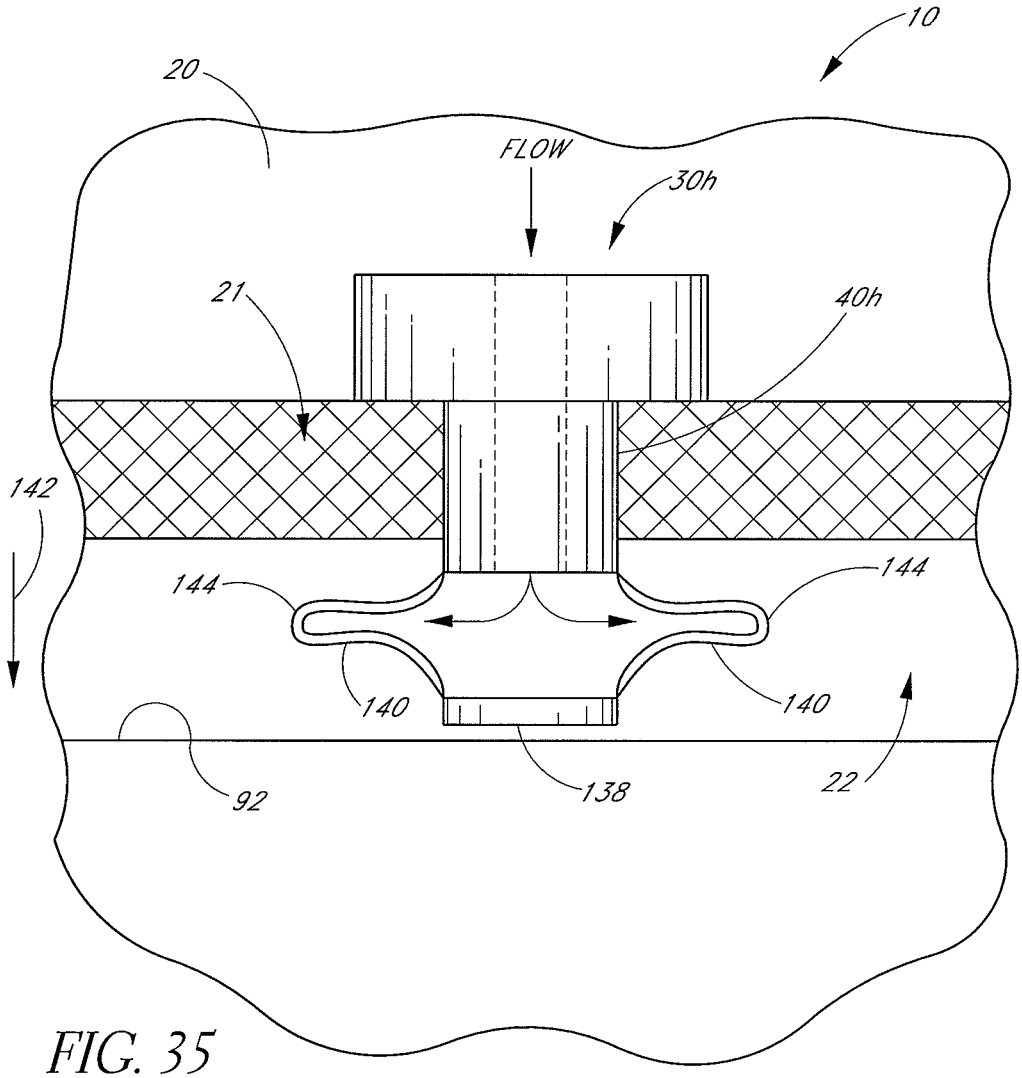

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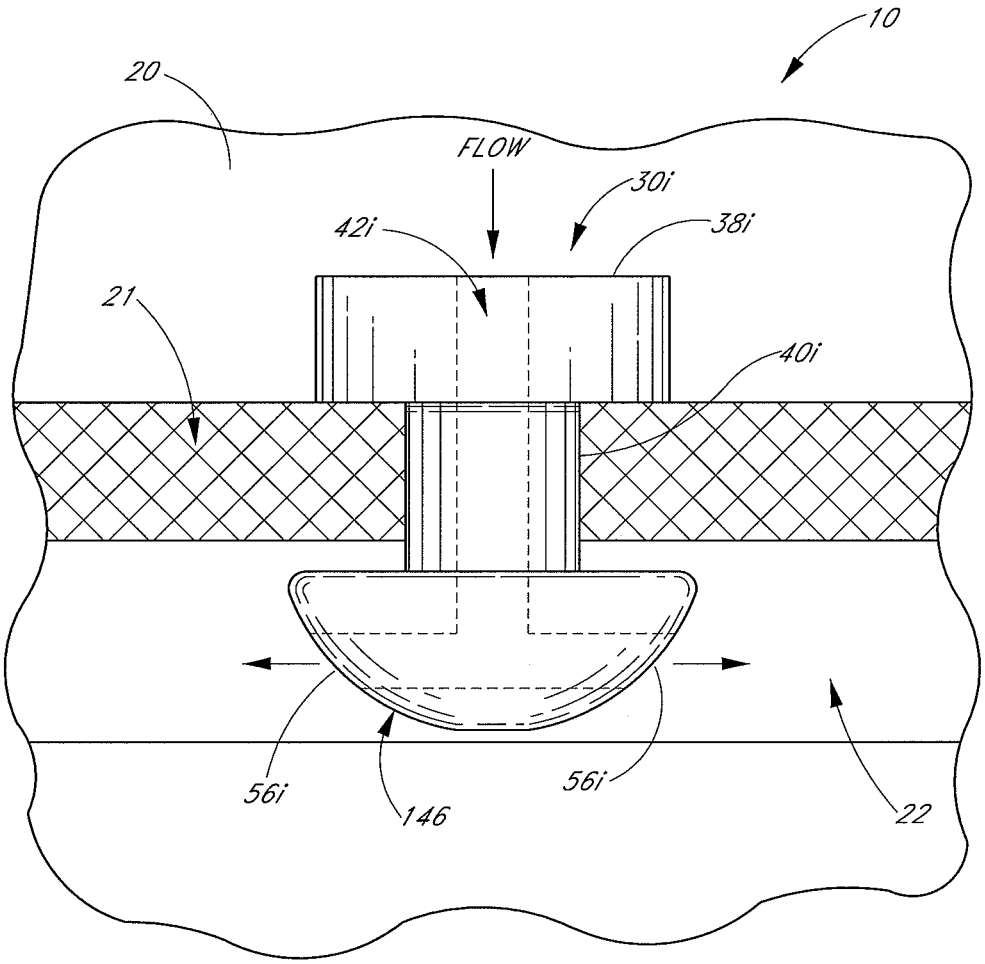

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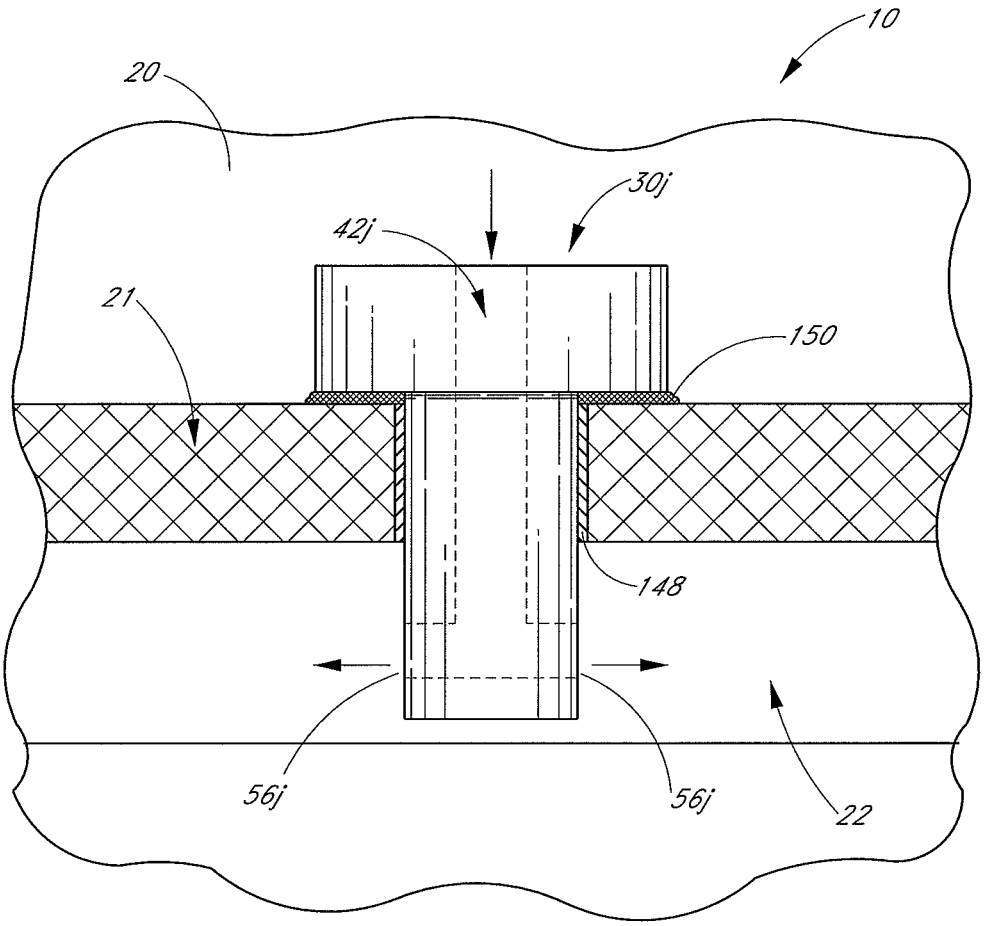

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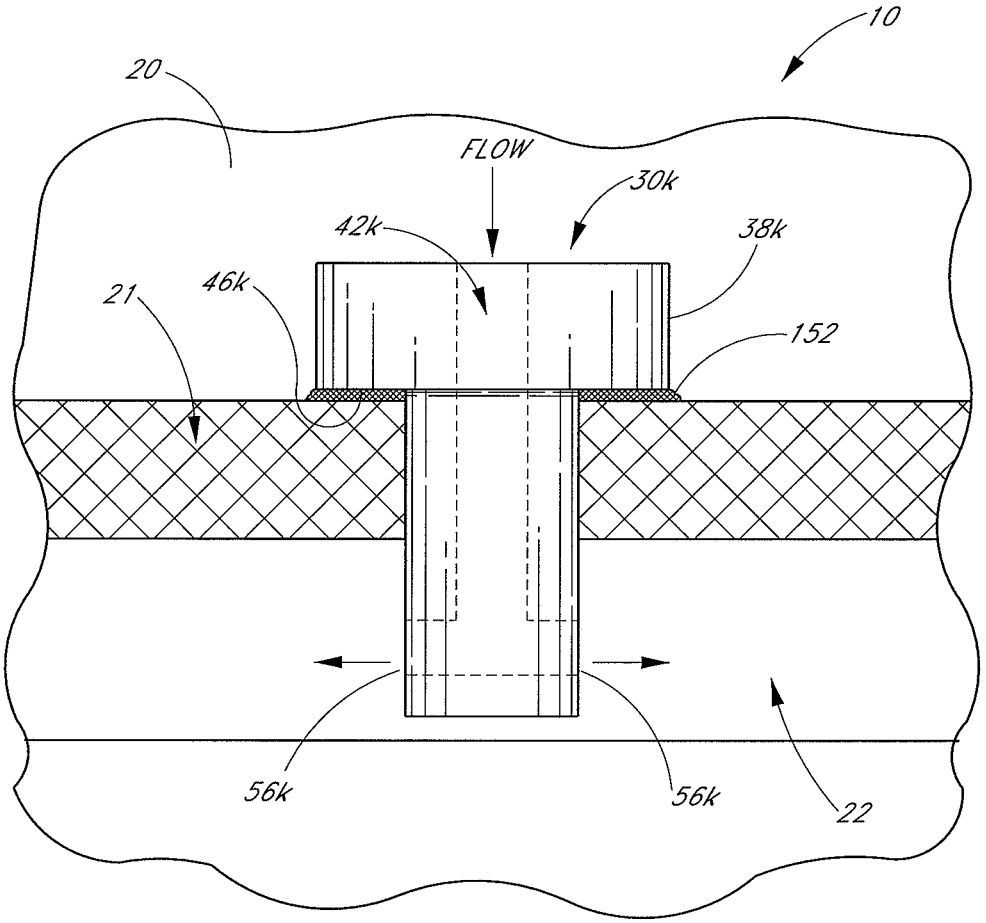

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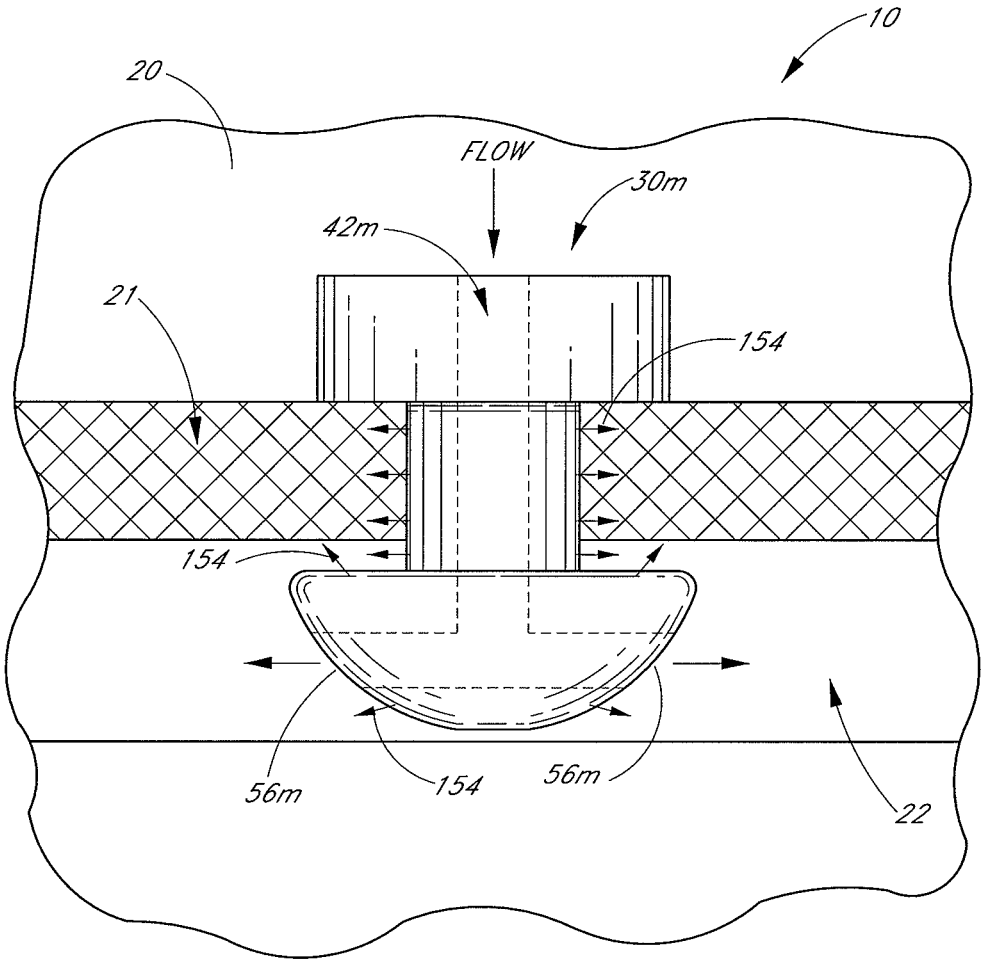

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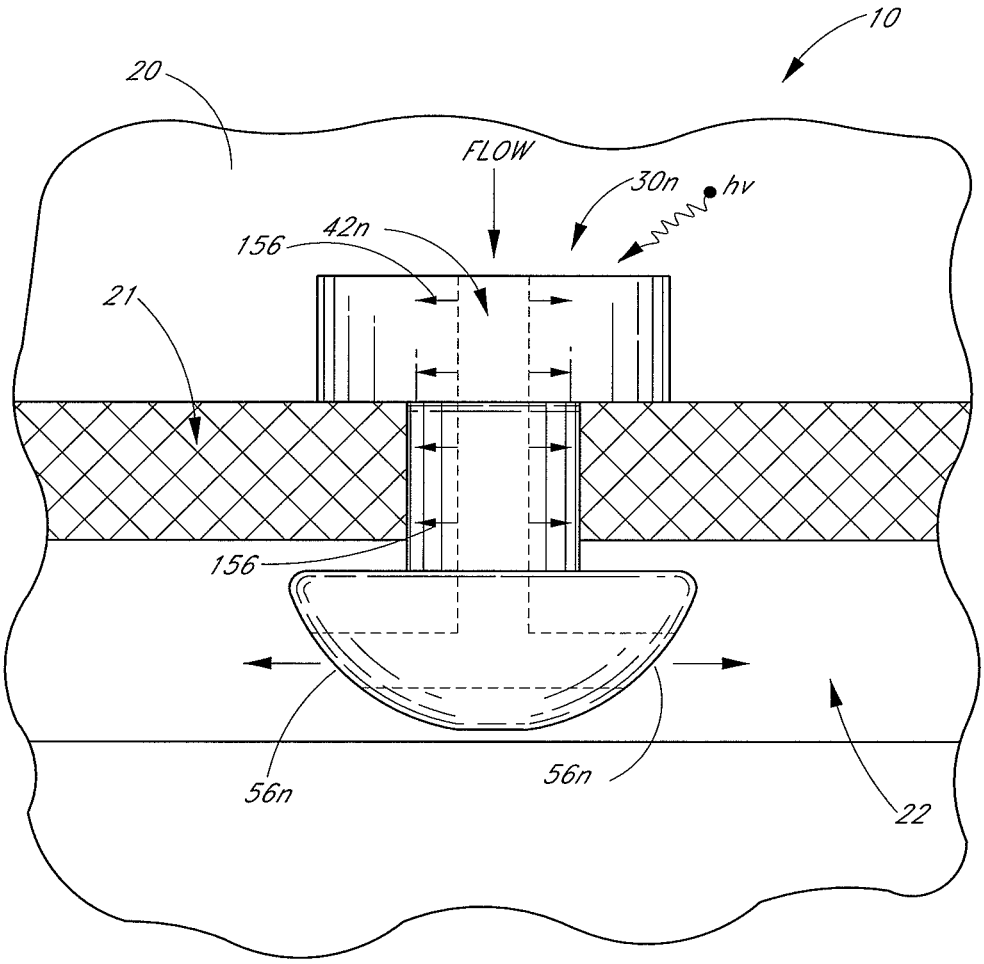

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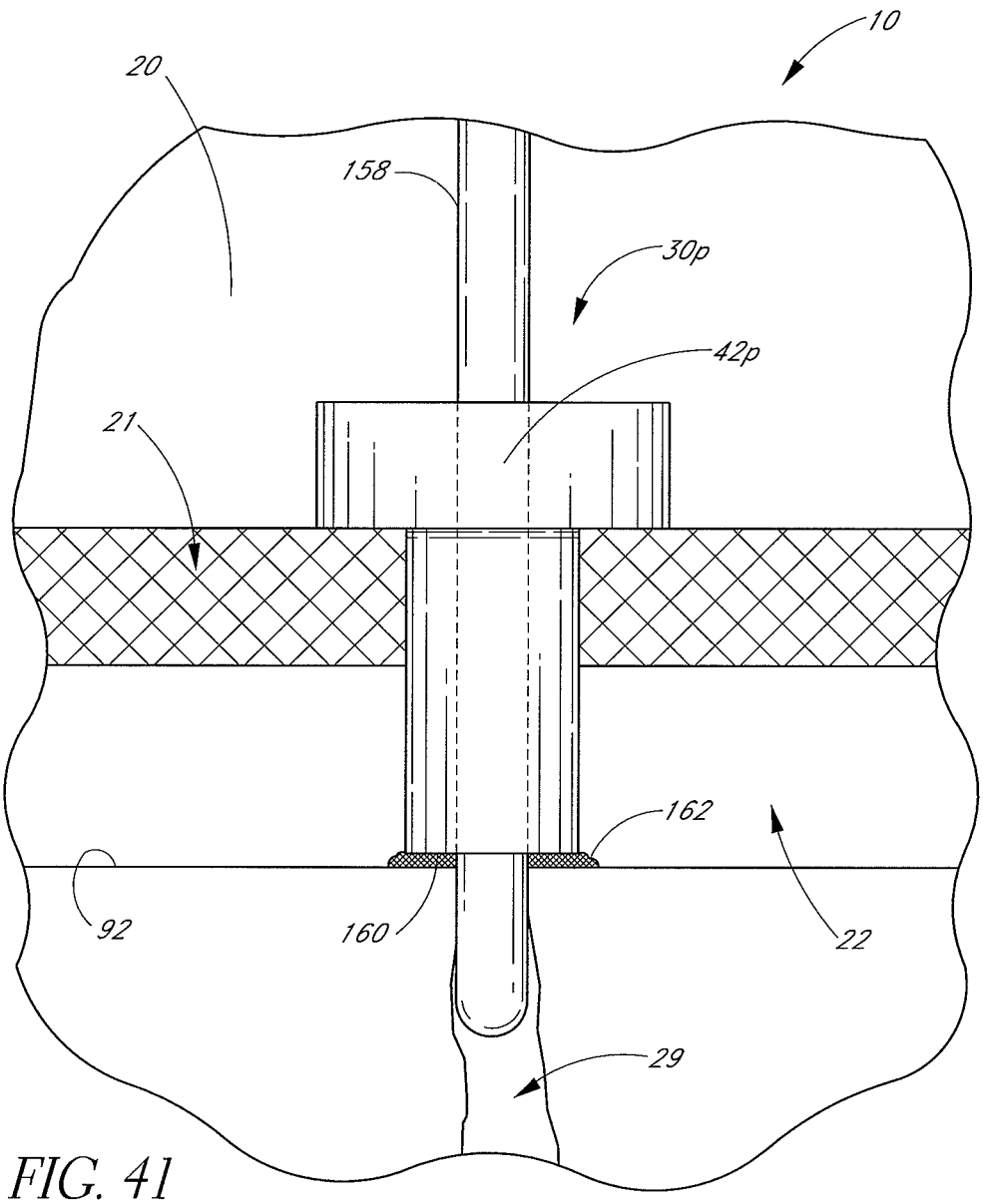

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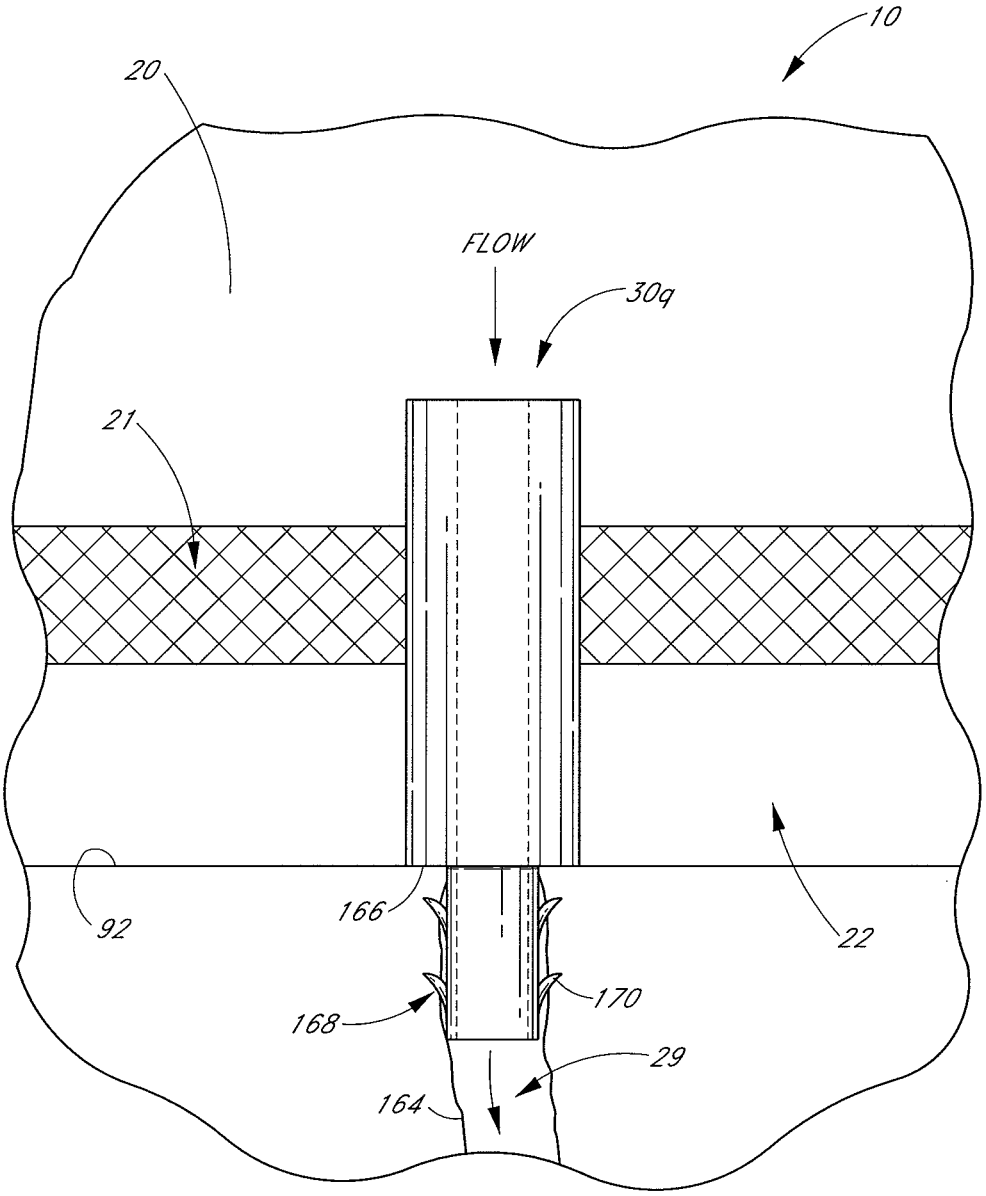

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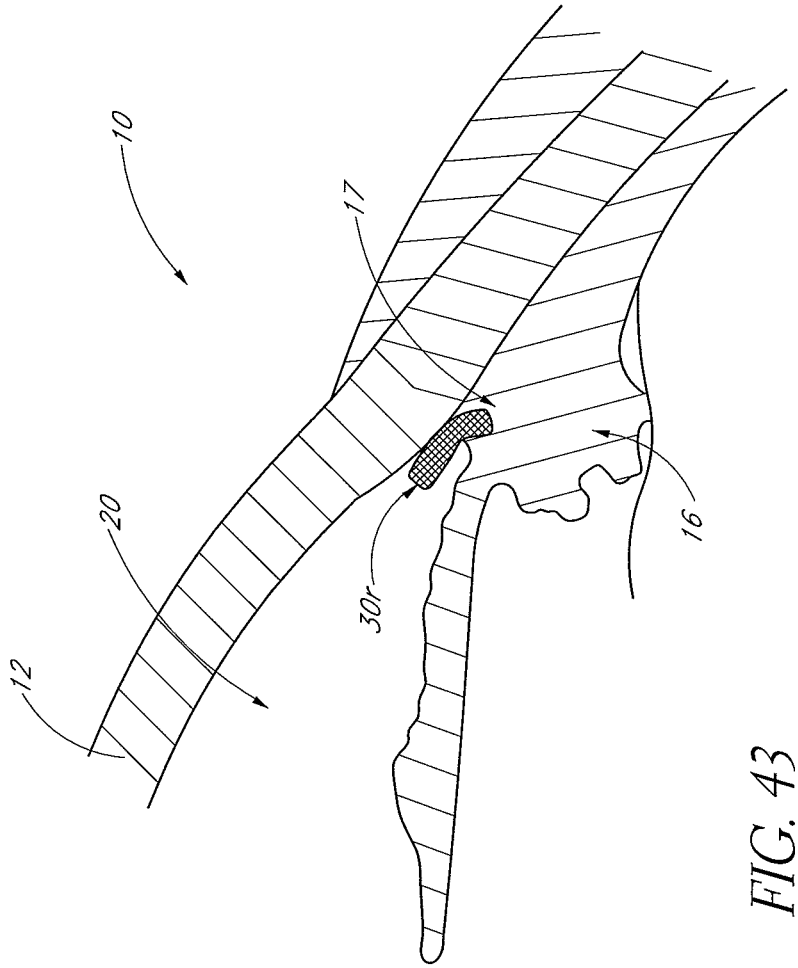

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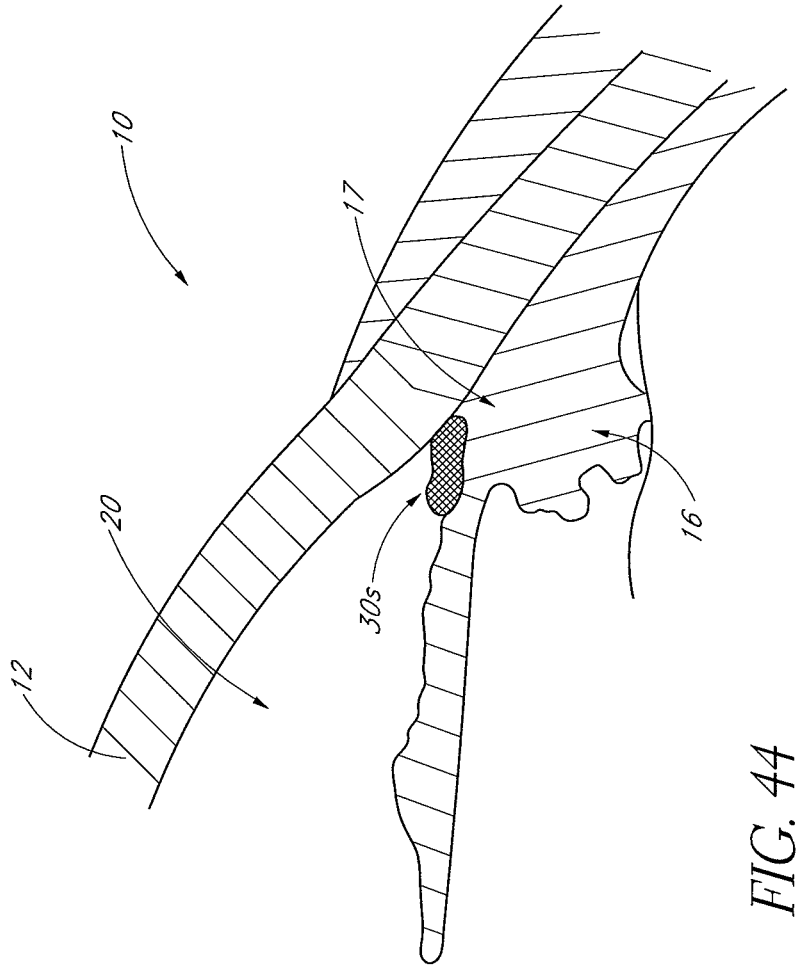

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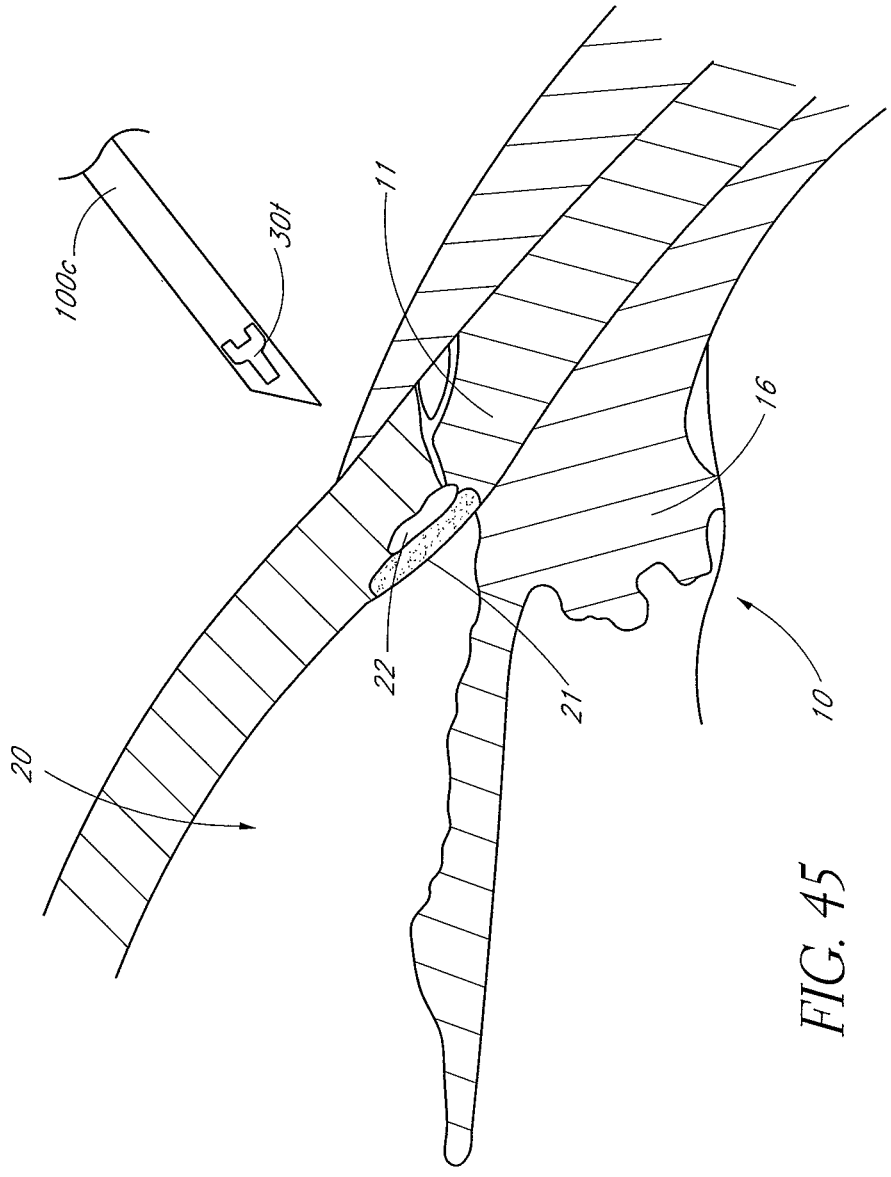

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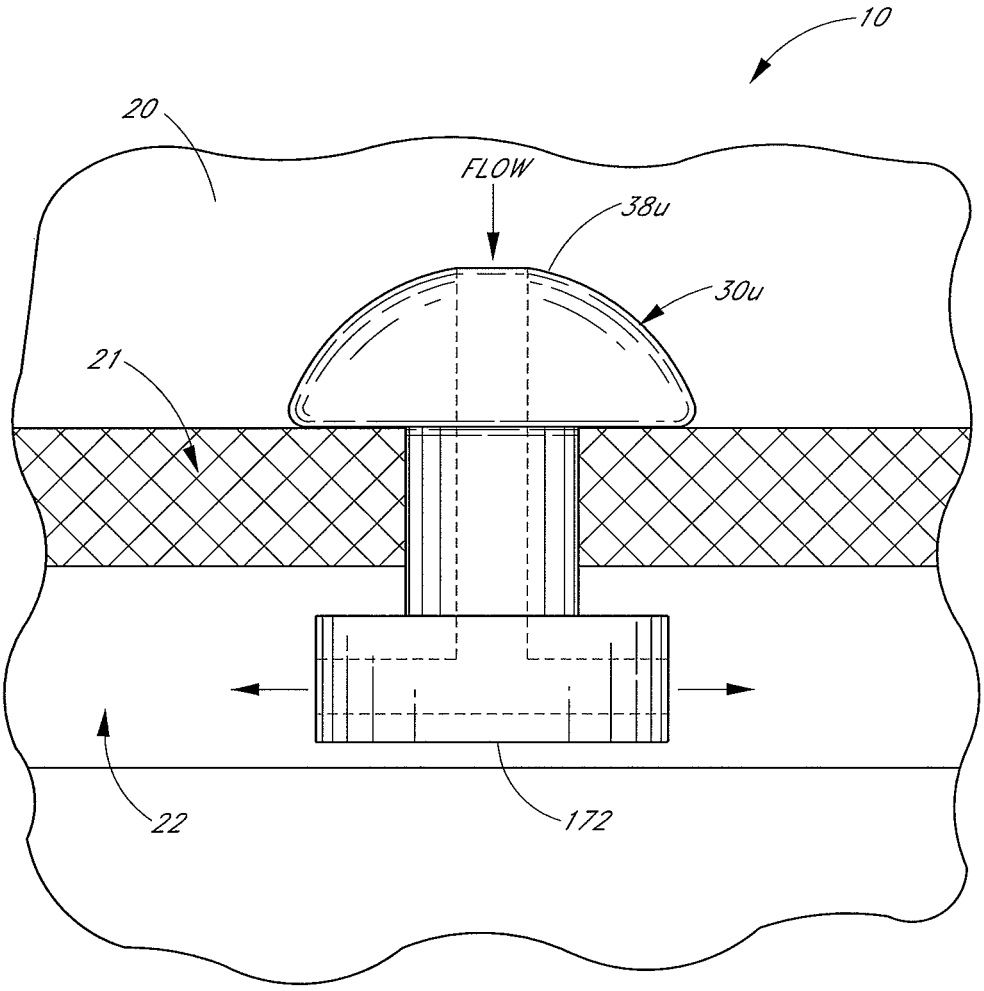

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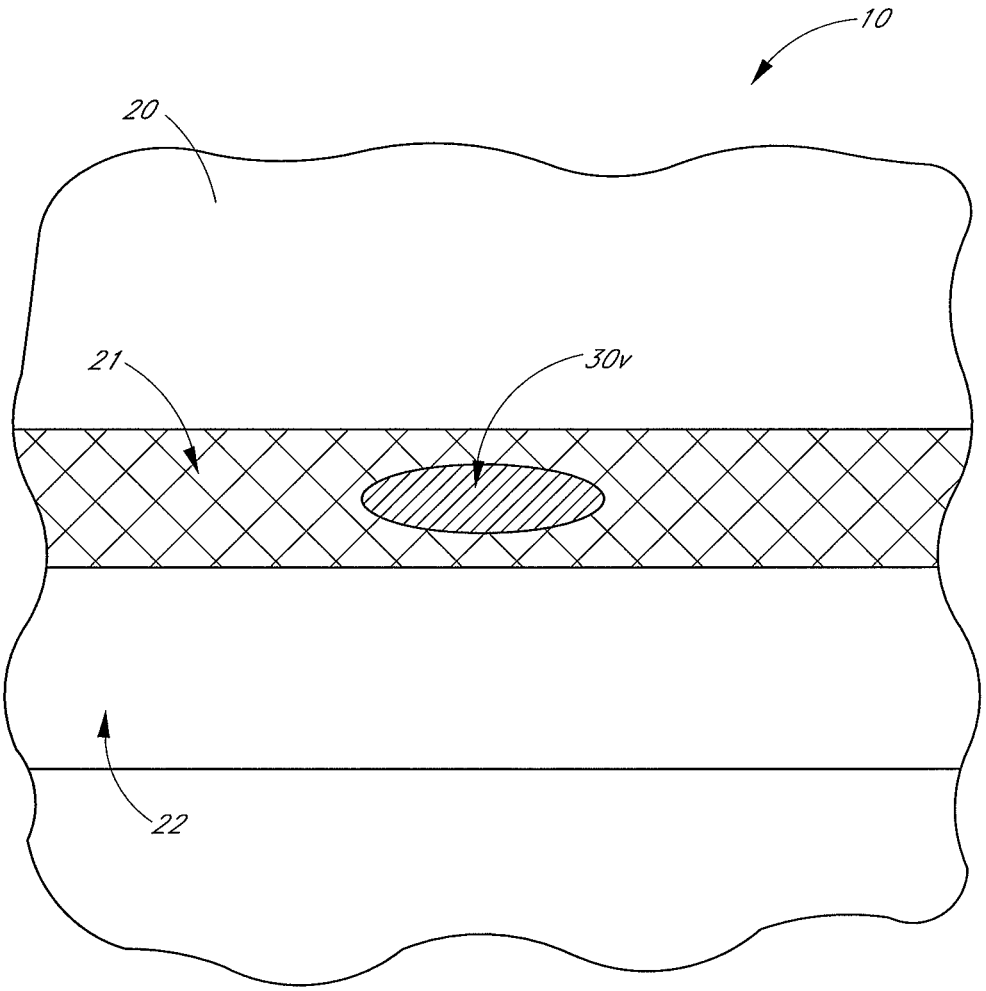


FIG. 47

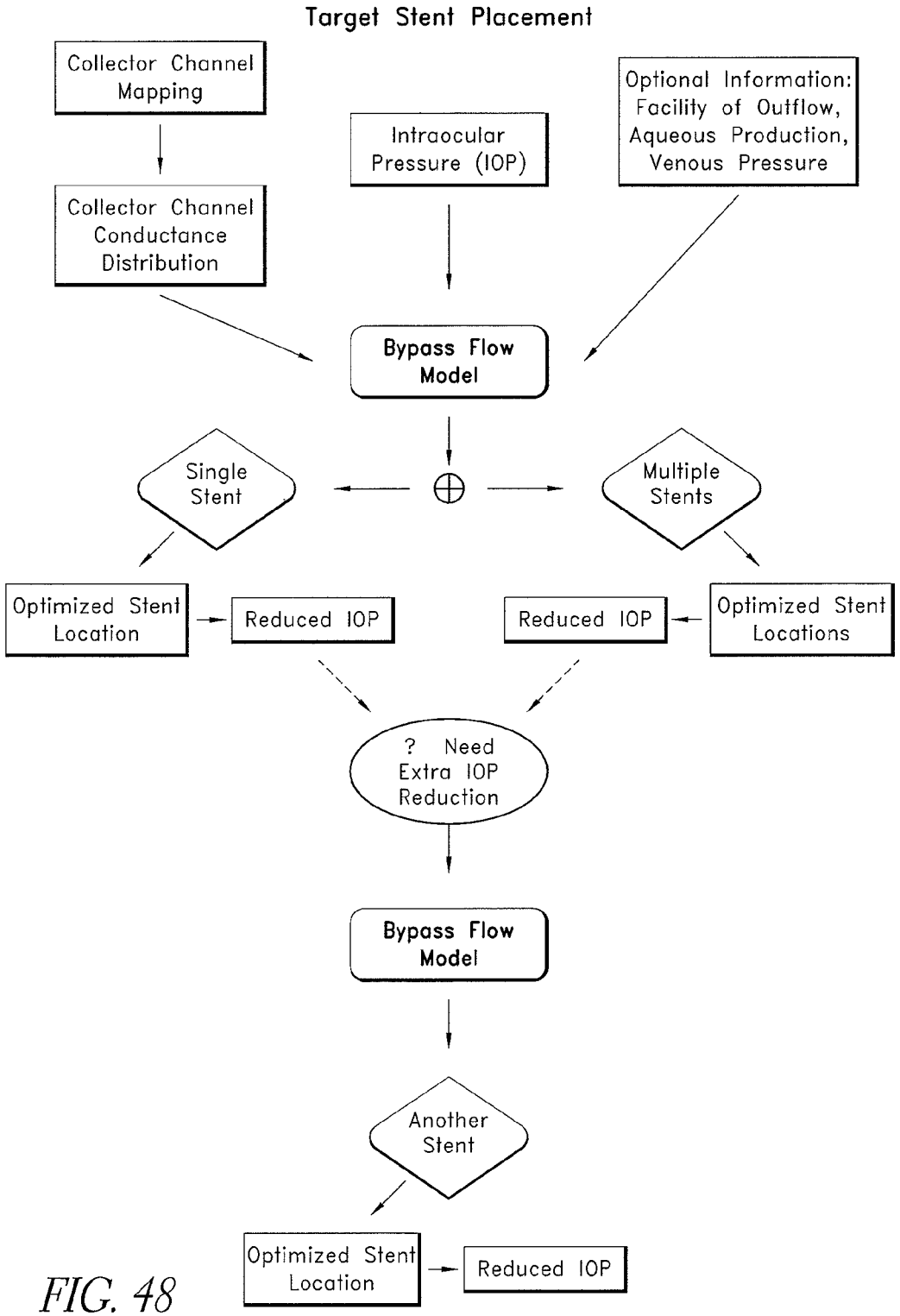

Target Stent Placement
Collector Channel Mapping
Collector Channel Conductance Distribution
Intraocular Pressure (IOP)
Optional Information: Facility of Outflow, Aqueous Production, Venous Pressure
Bypass Flow Model
Single Stent
Multiple Stents
Optimized Stent Location
Reduced IOP
Reduced IOP
Optimized Stent Locations
? Need Extra IOP Reduction
Bypass Flow Model
Another Stent
Optimized Stent Location
Reduced IOP

FIG. 48

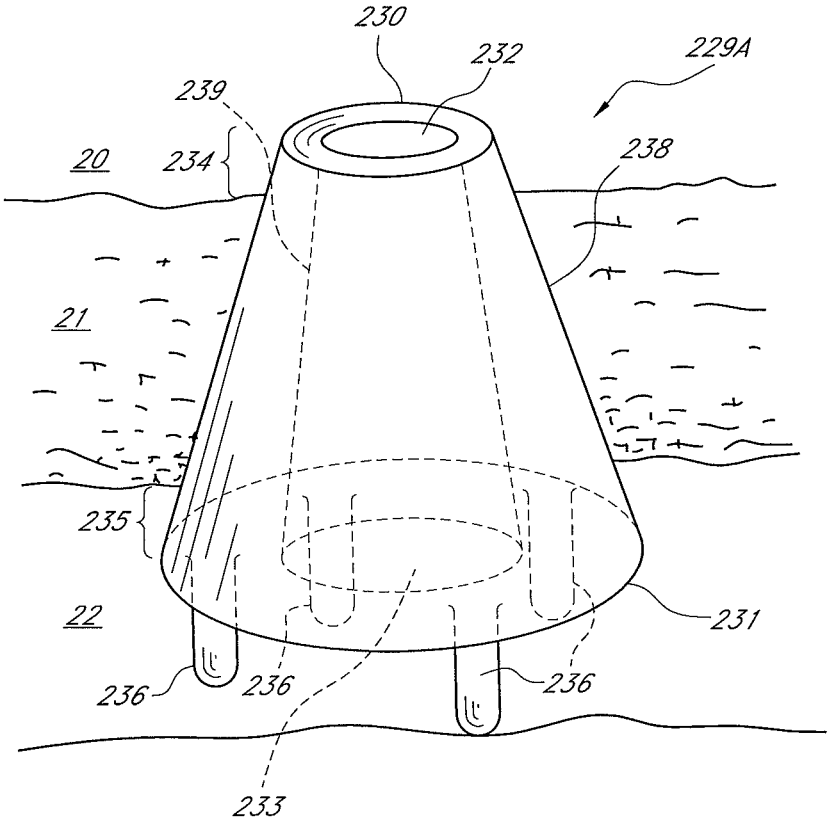


FIG. 49A

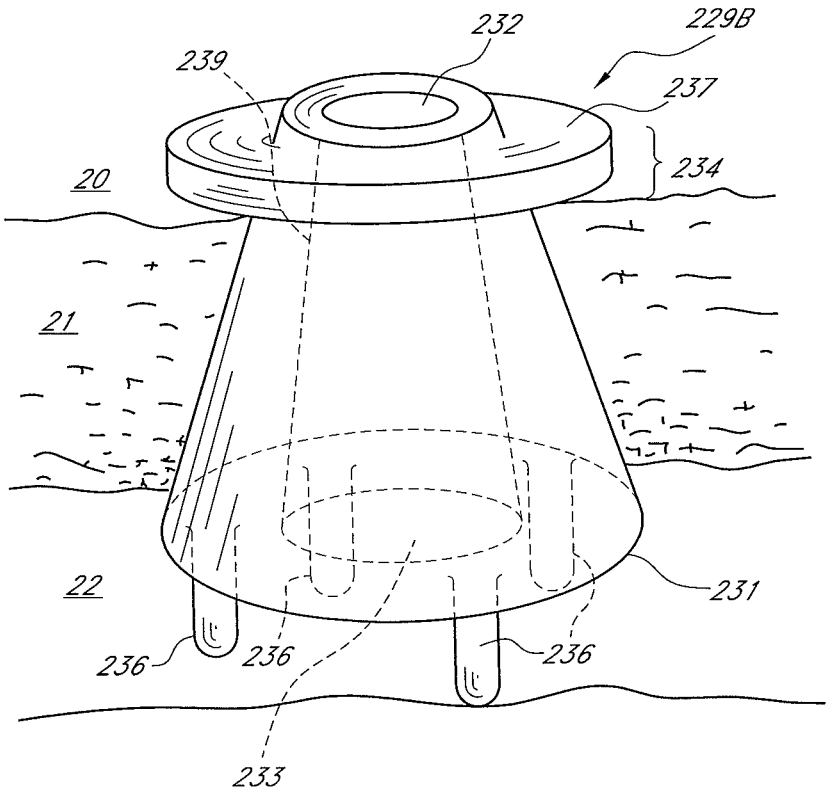


FIG. 49B

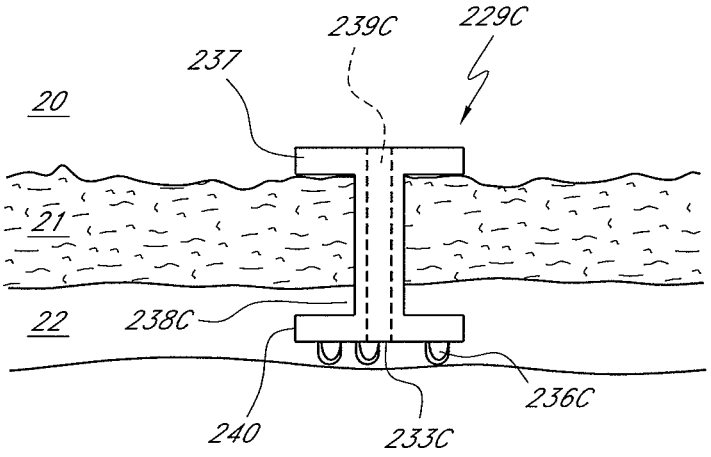


FIG. 49C

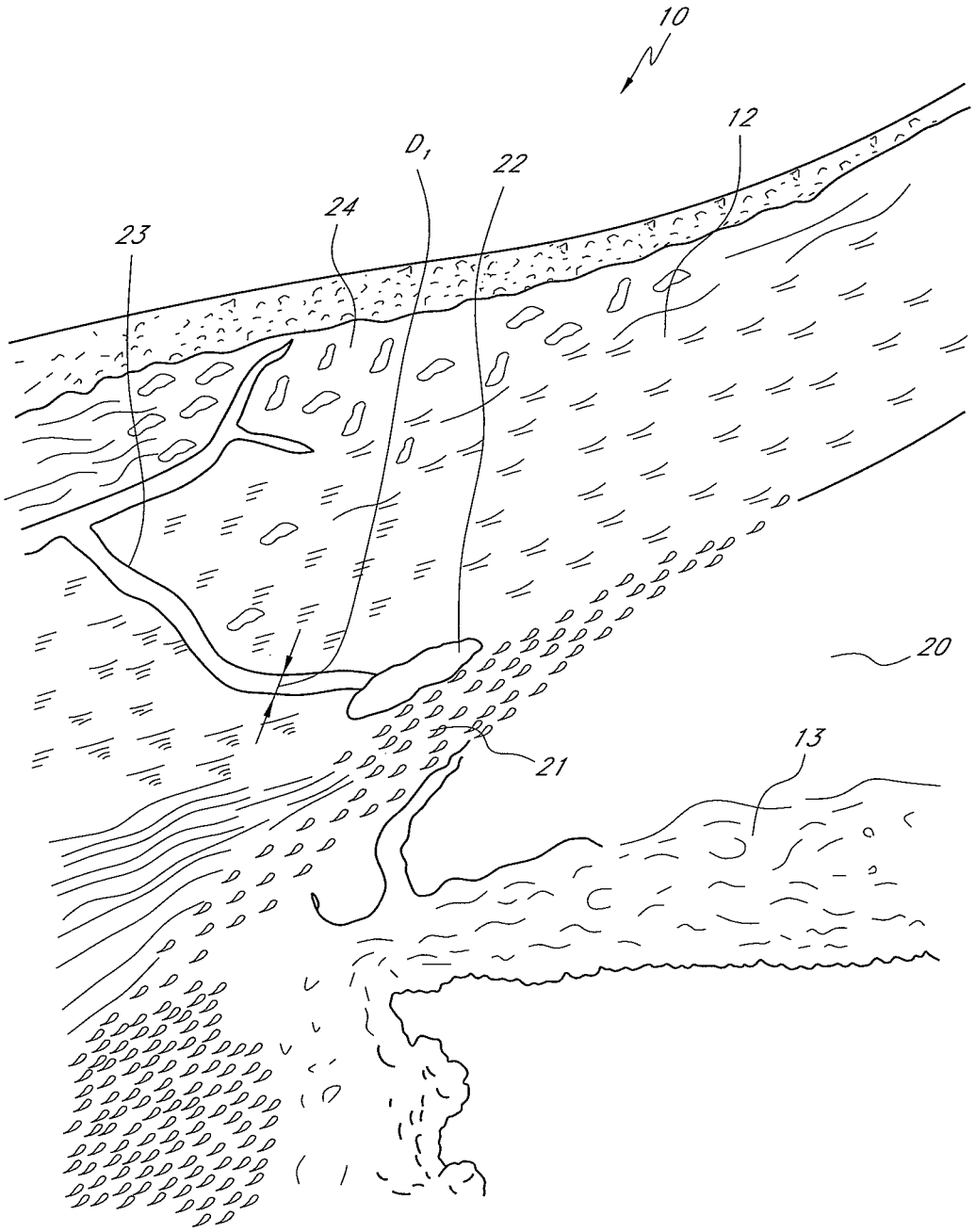


FIG. 50A

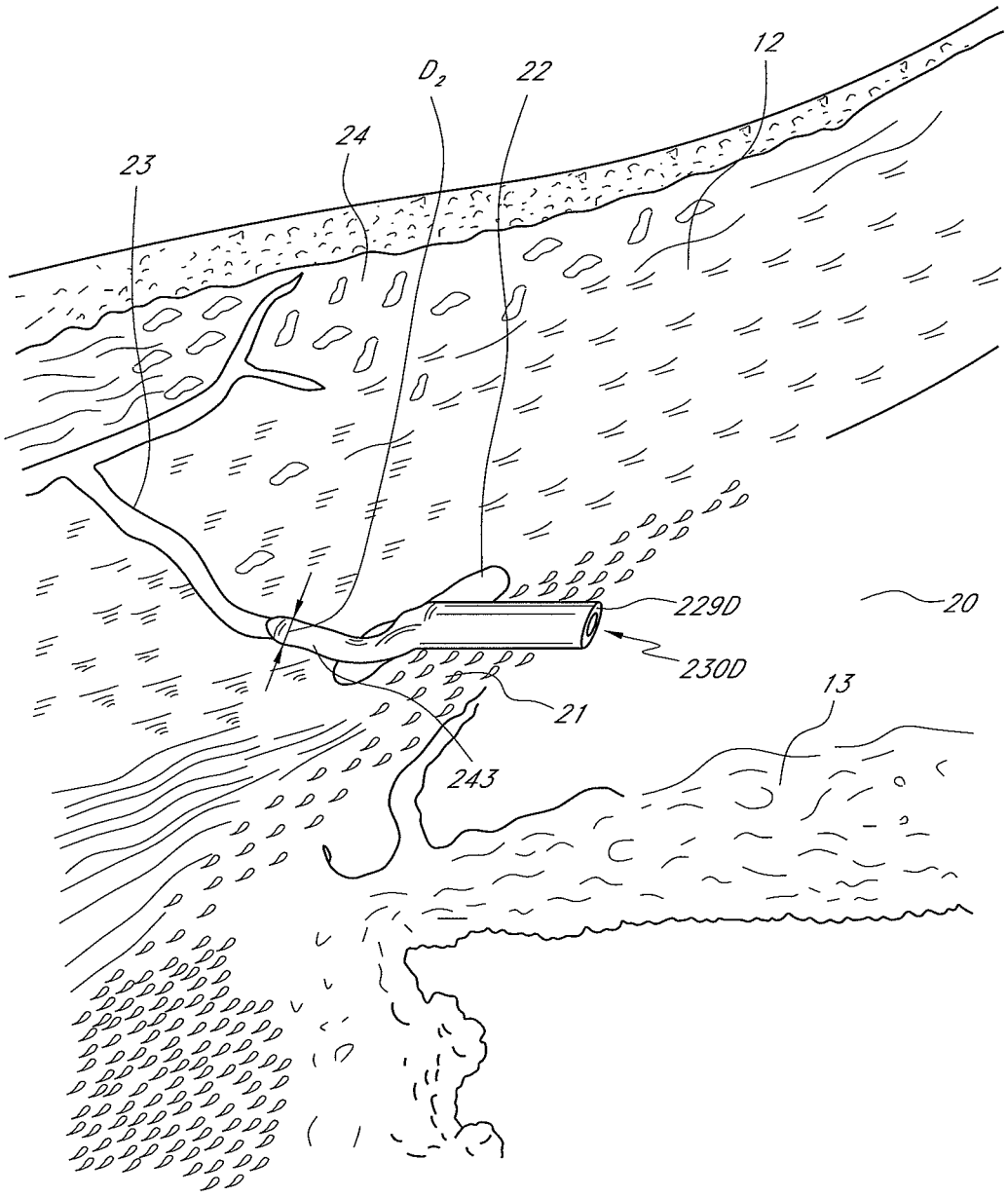
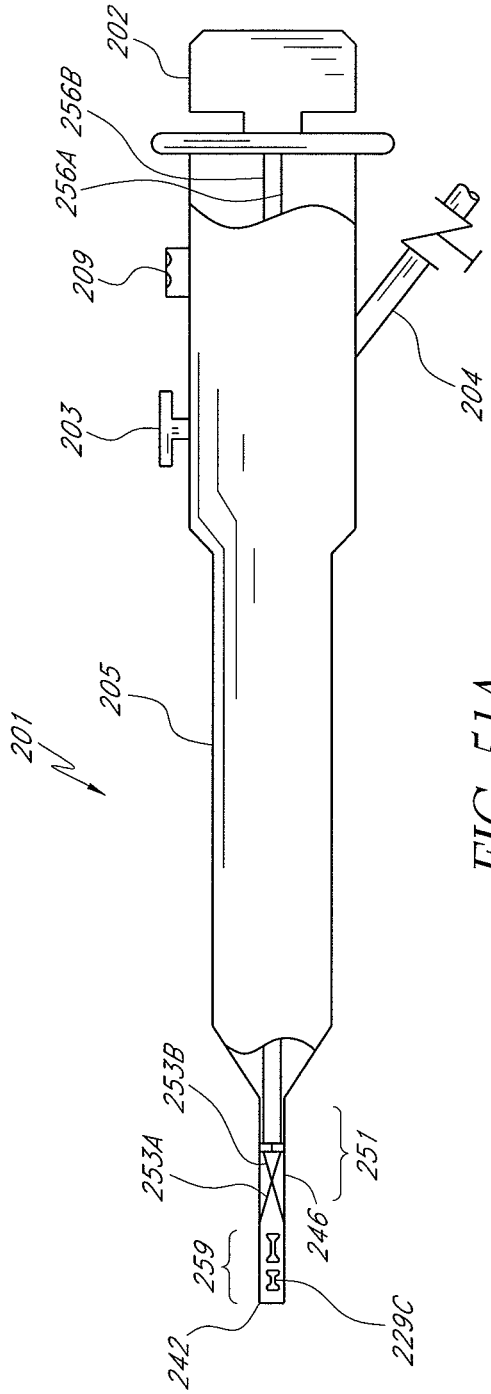


FIG. 50B


202
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229C

FIG. 51A

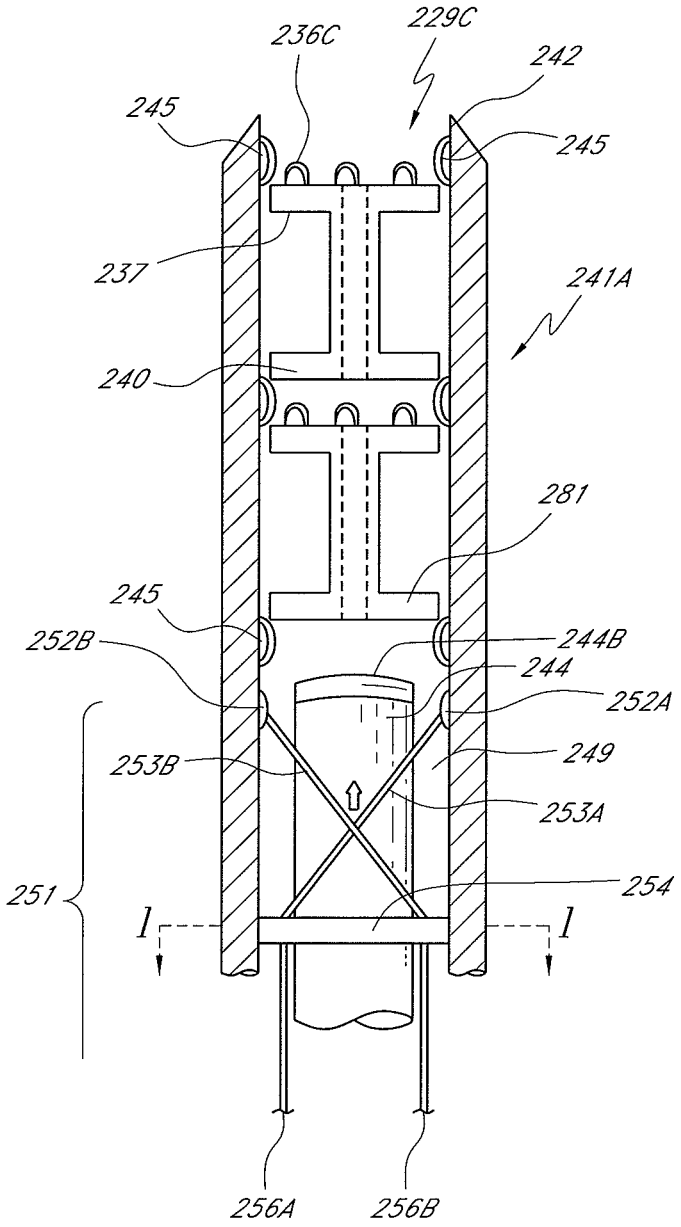
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FIG. 51B

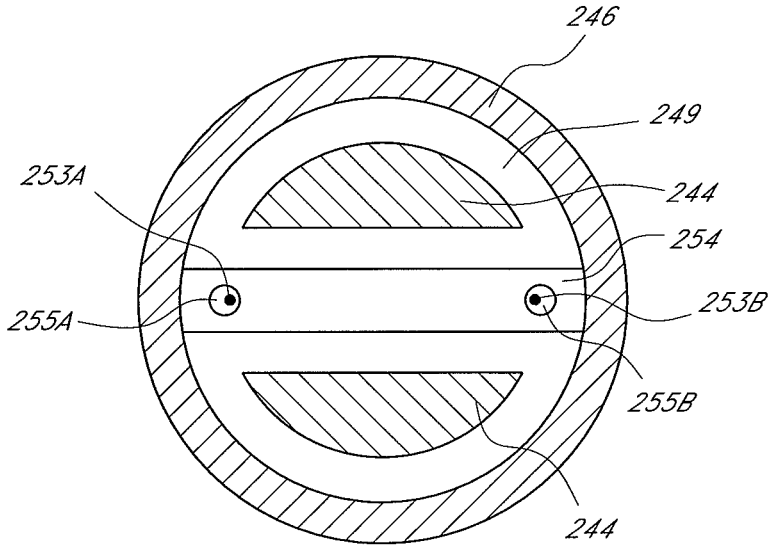

FIG. 51C

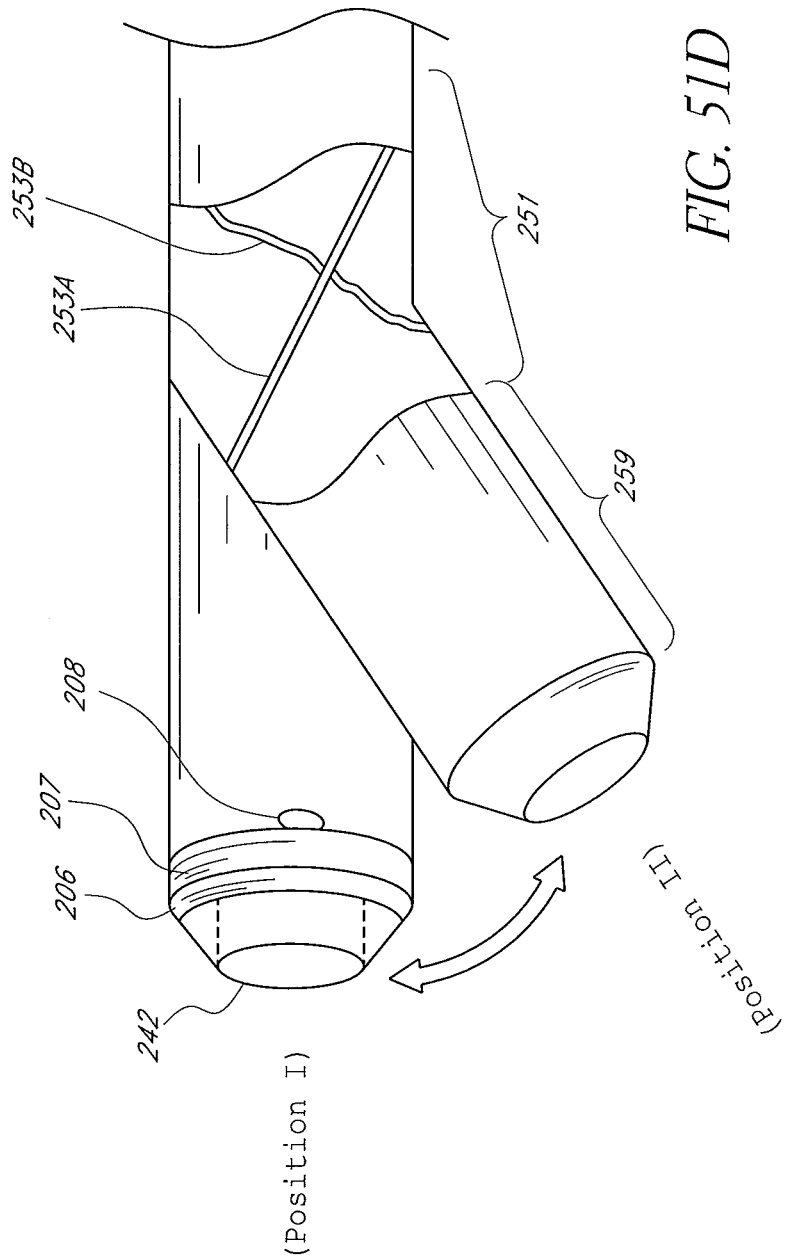

FIG. 51D

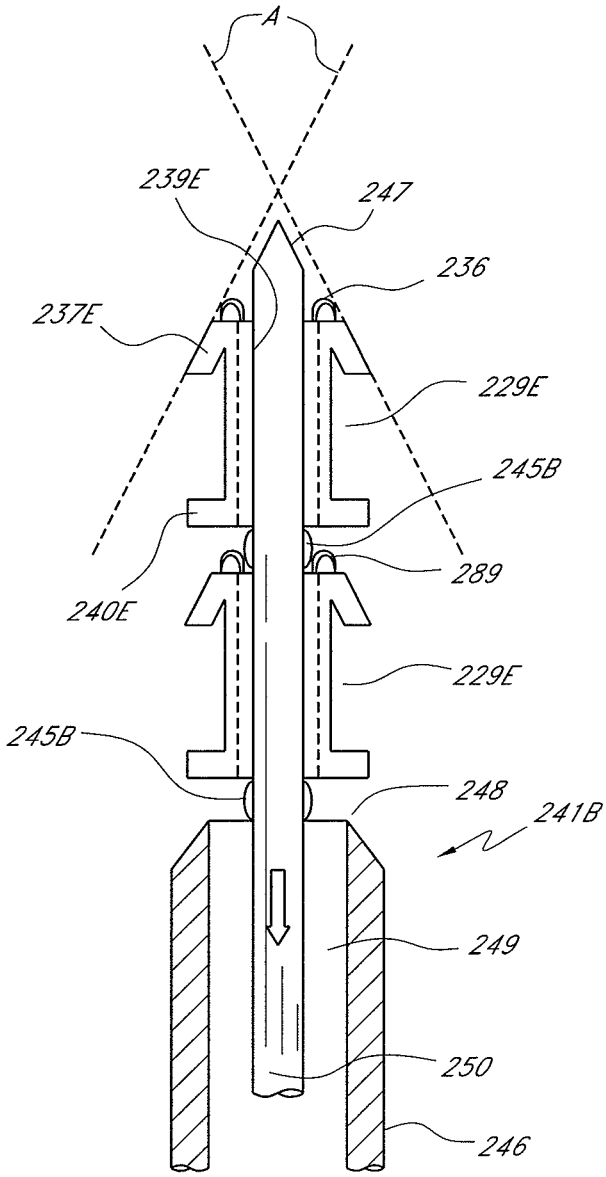
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FIG. 52A

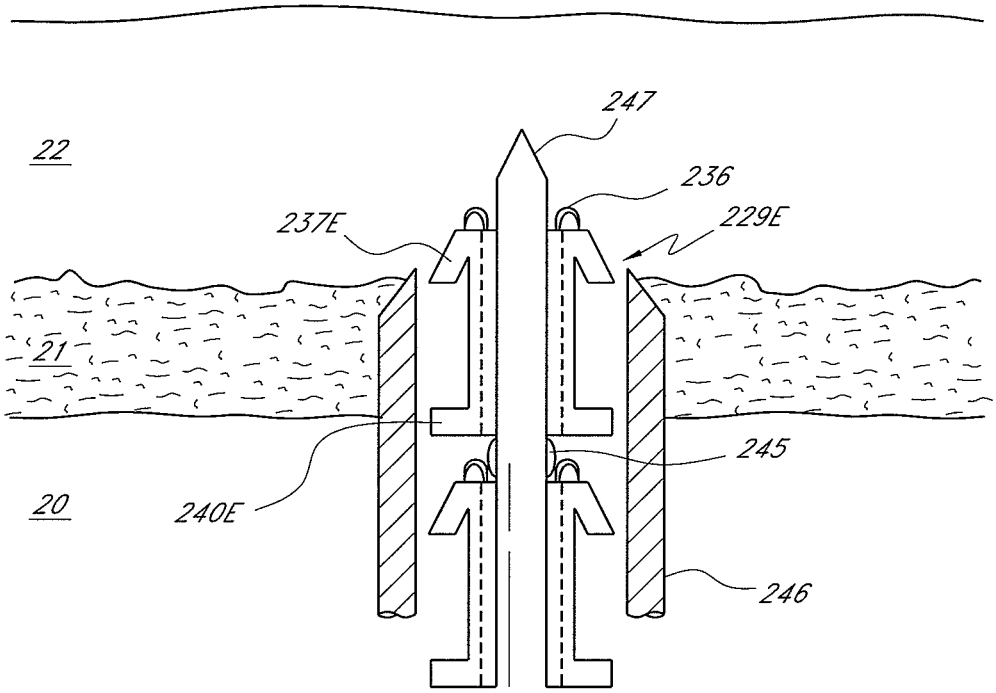

FIG. 52B

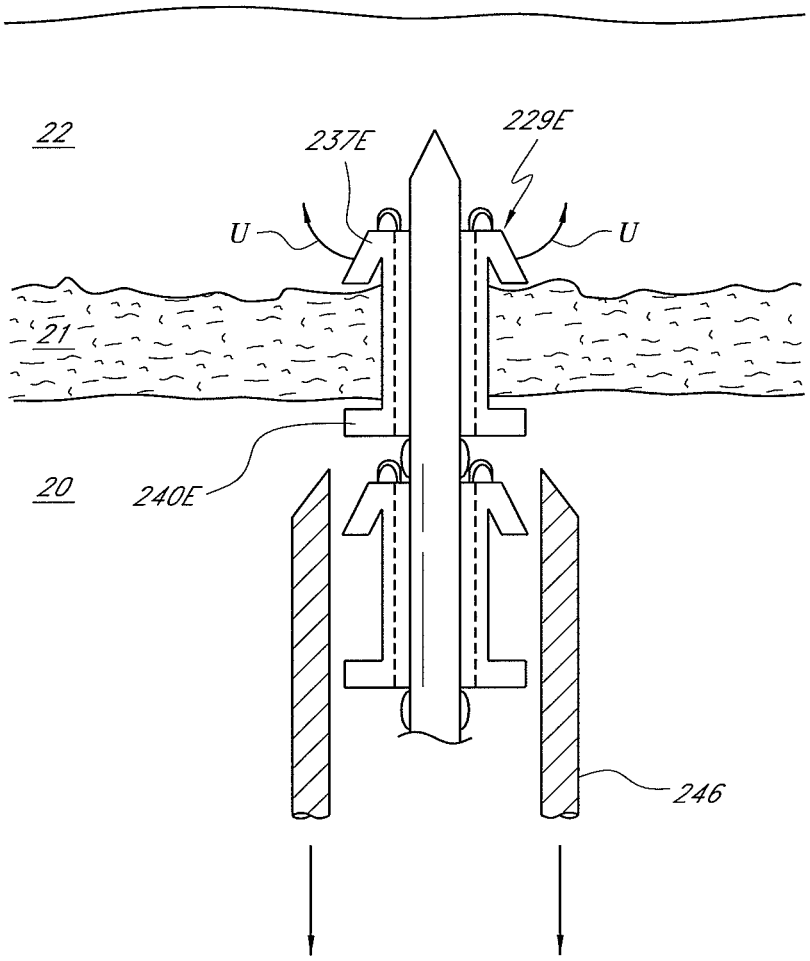

FIG. 52C

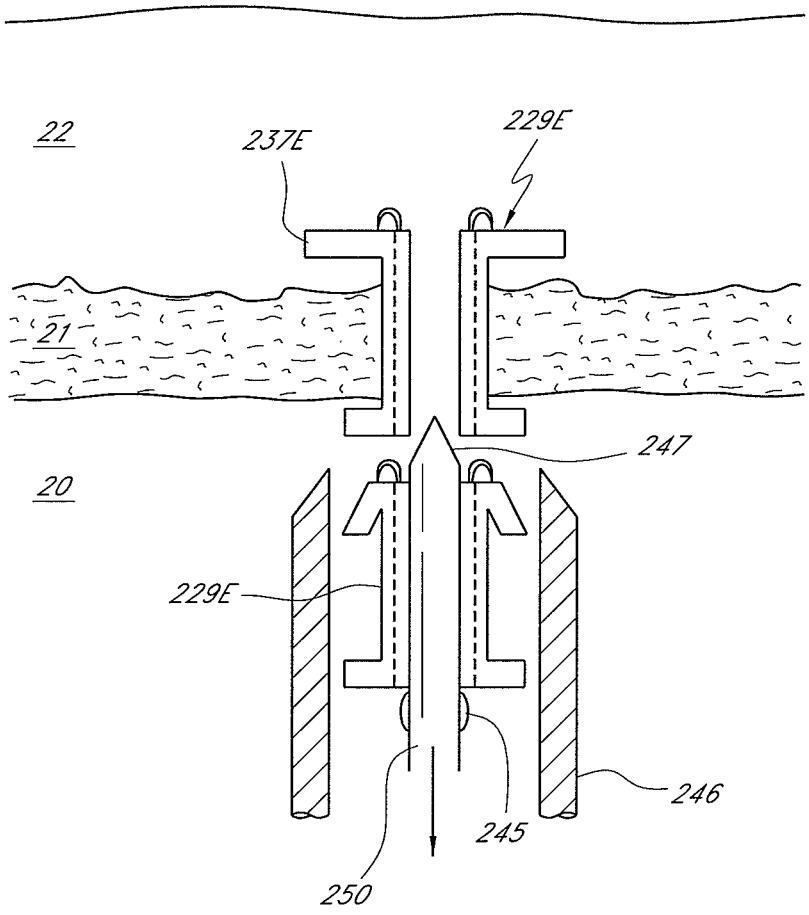

FIG. 52D

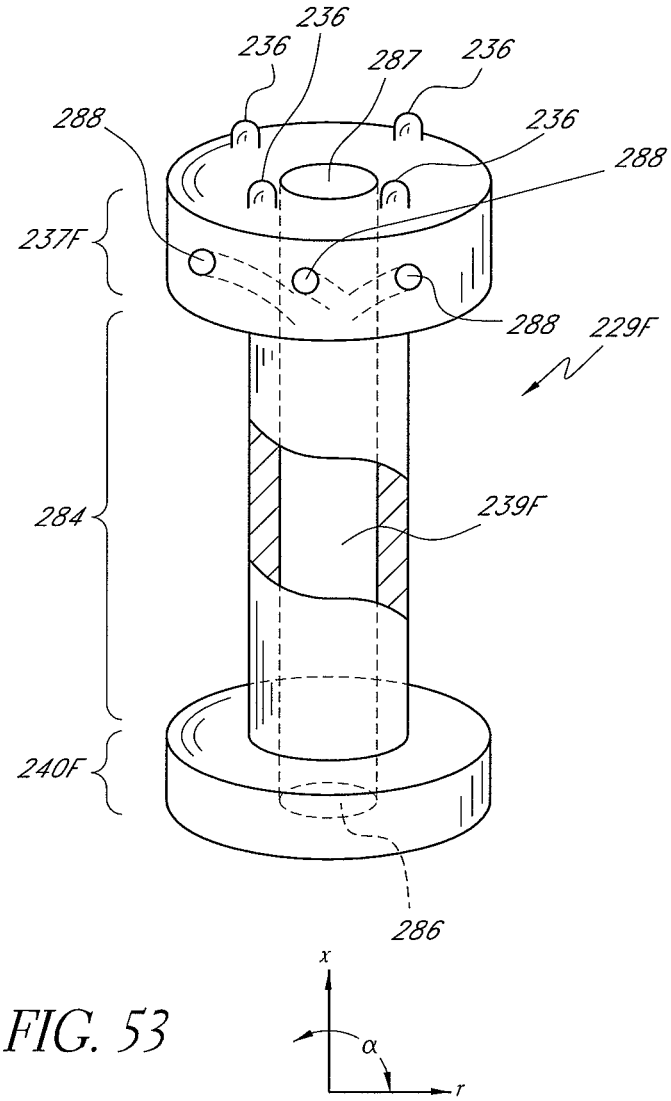

FIG. 53

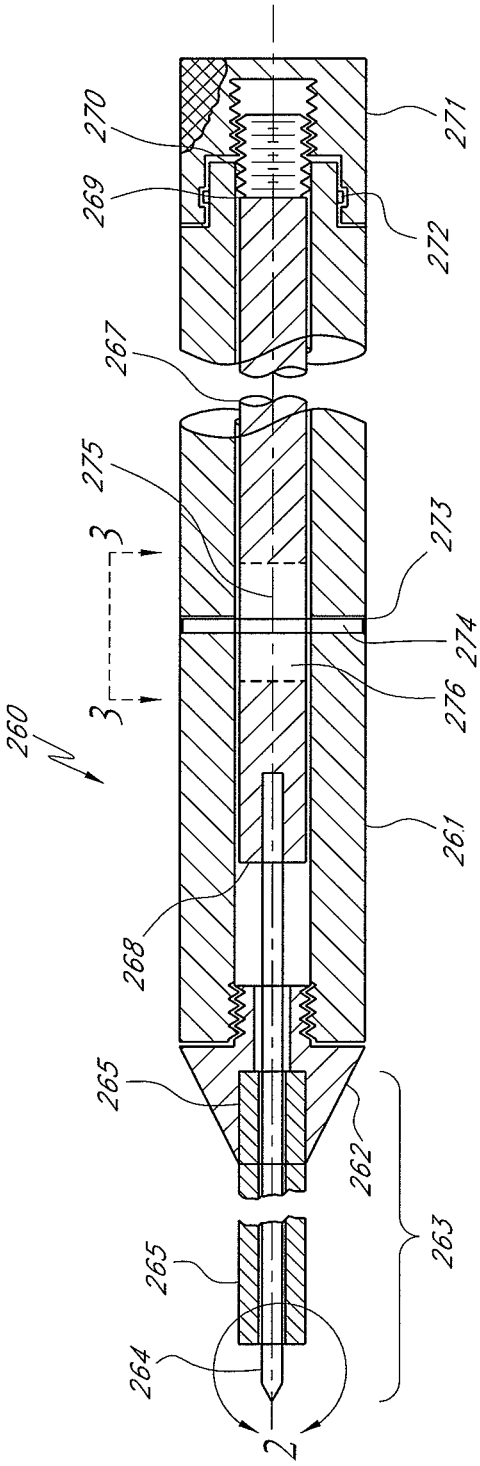
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FIG. 54A

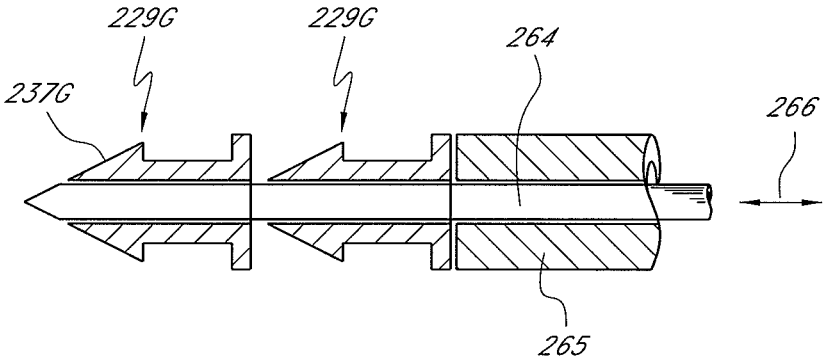

FIG. 54B

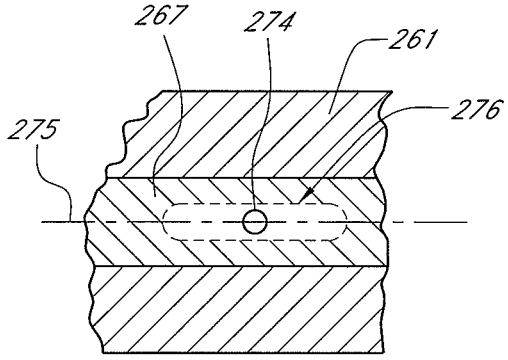

FIG. 54C

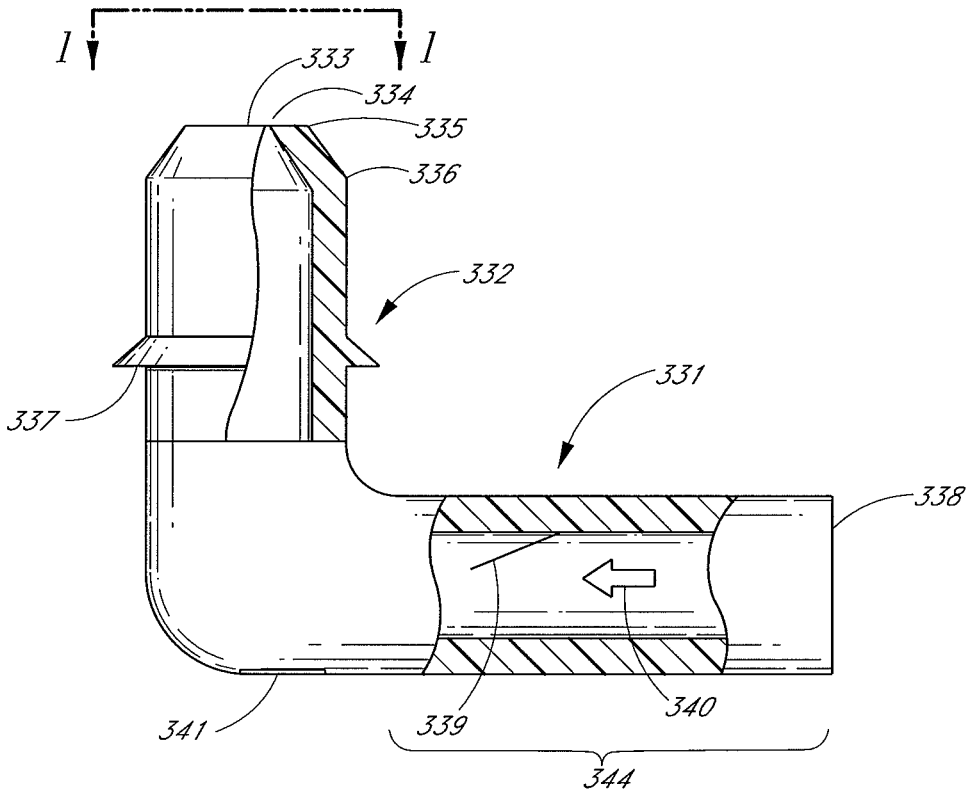
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FIG. 55

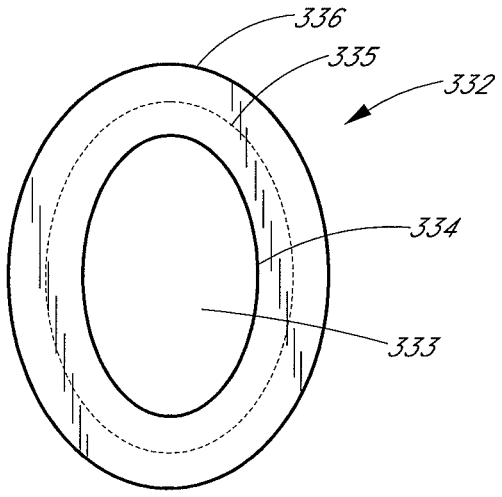
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FIG. 56

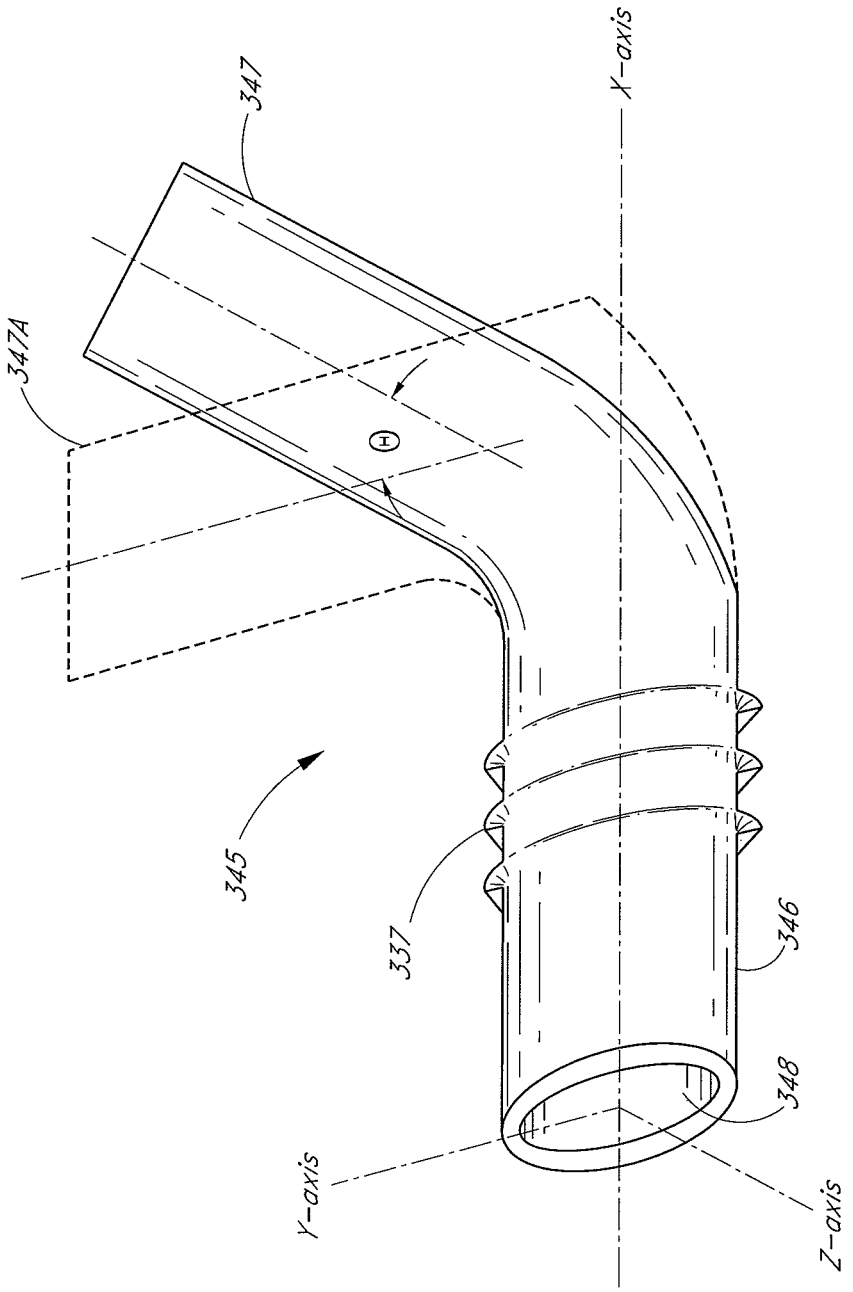

FIG. 57

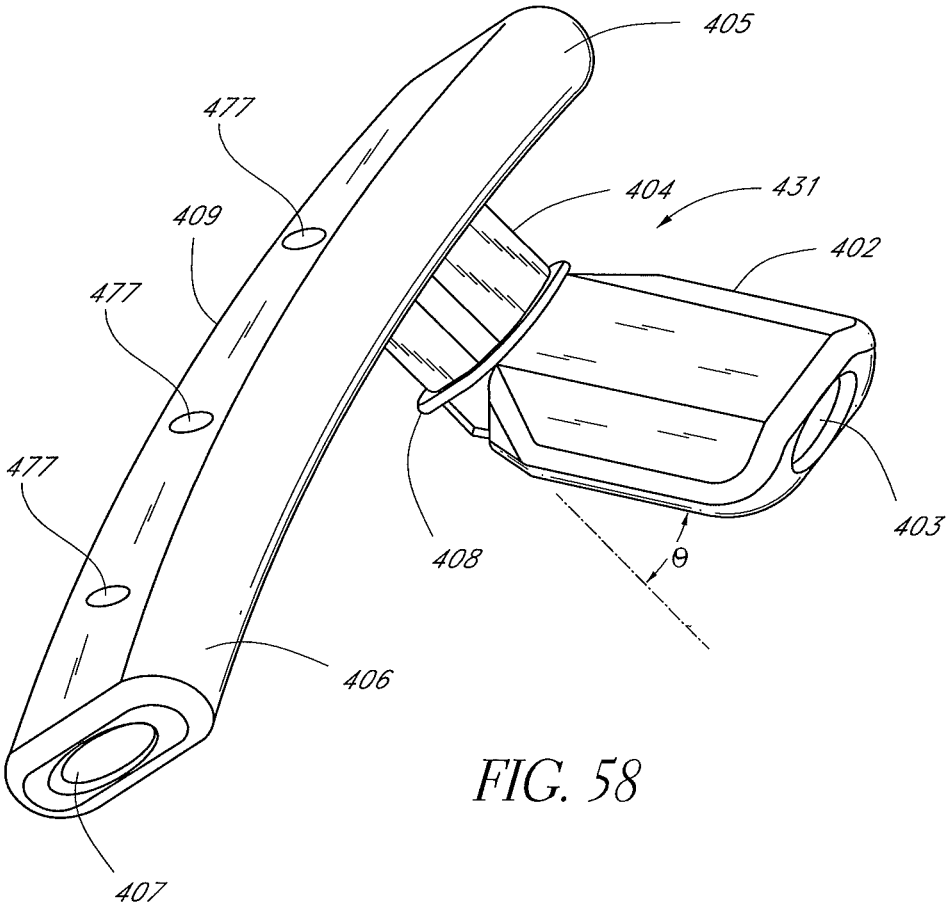

FIG. 58

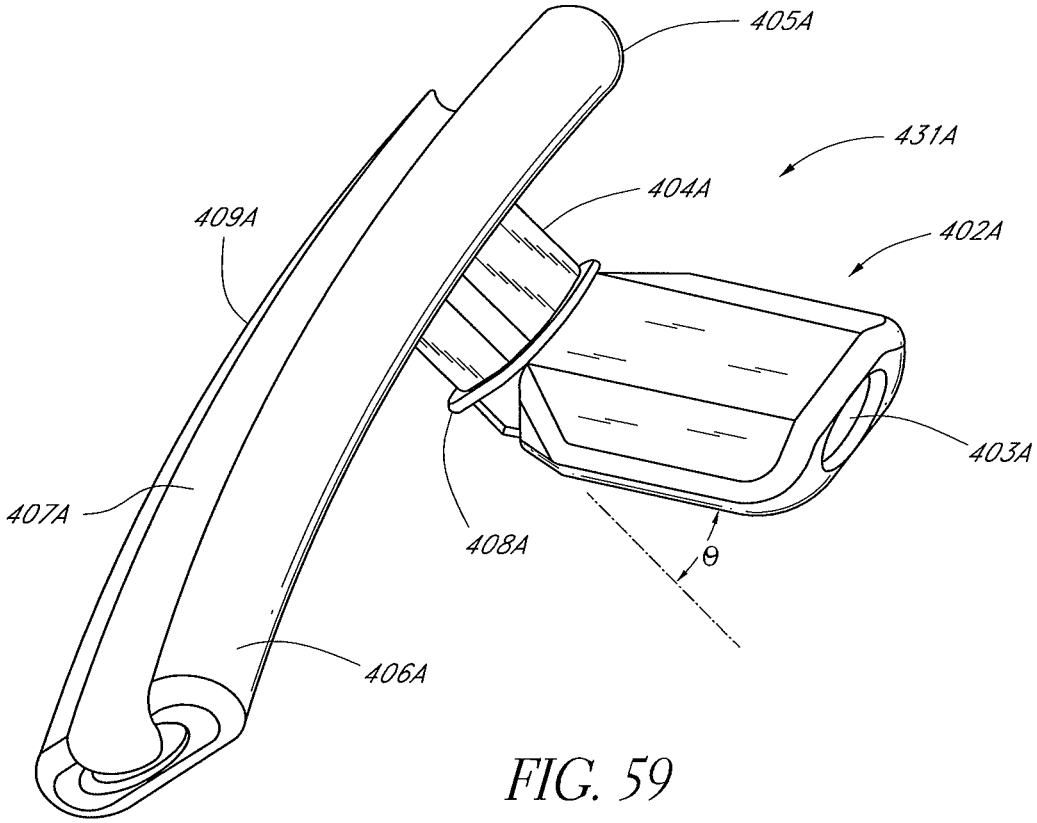

FIG. 59

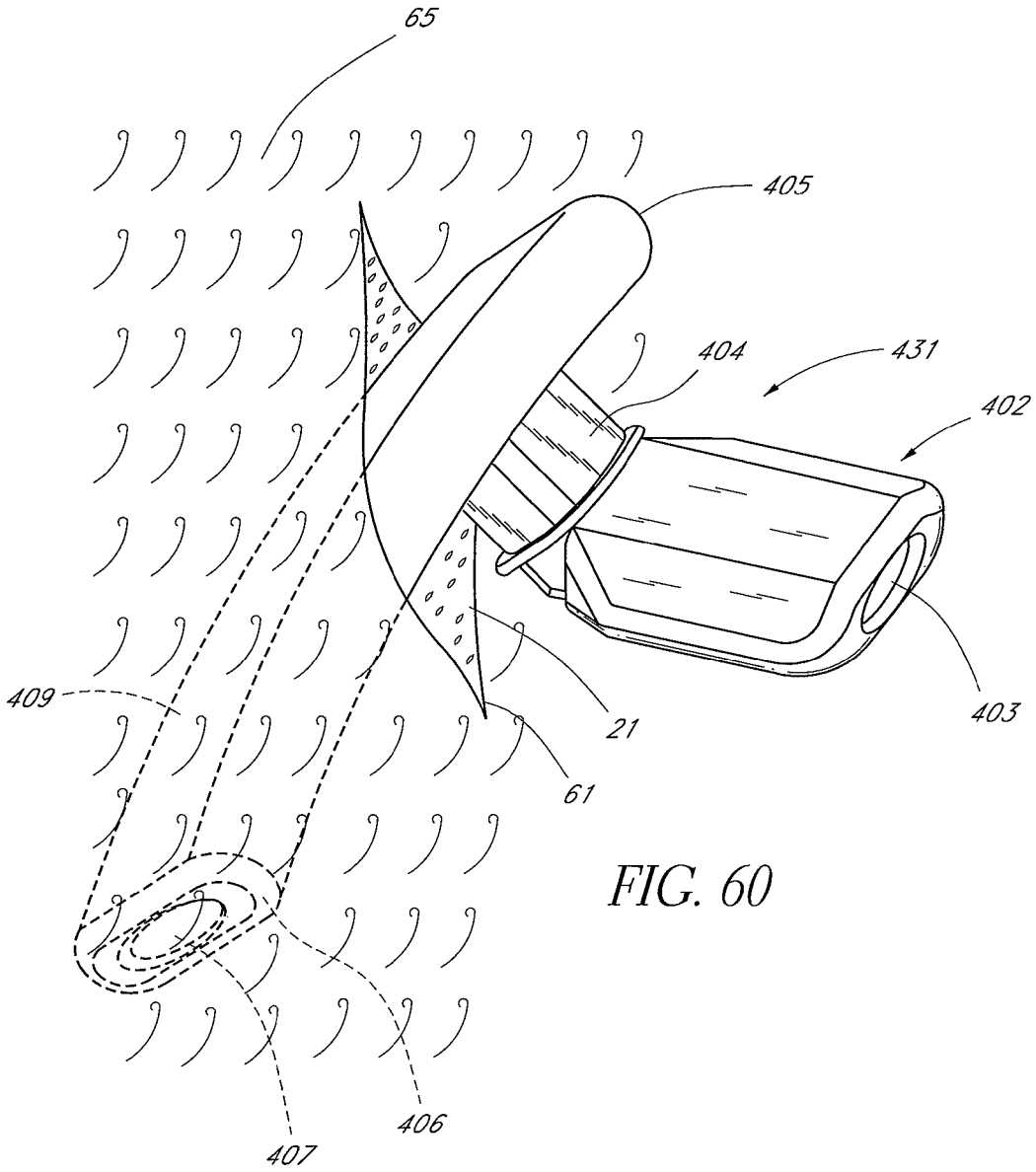

FIG. 60

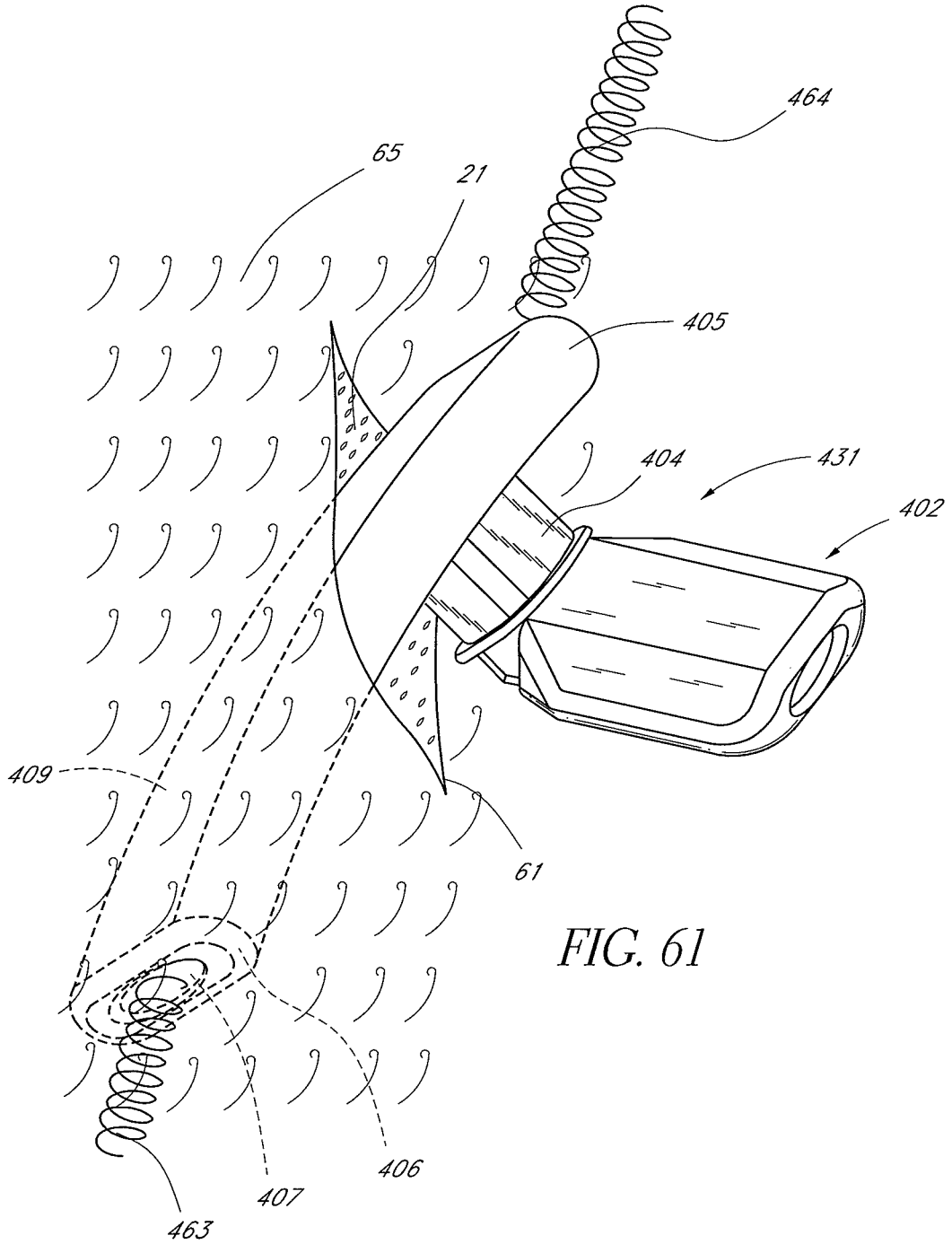

FIG. 61

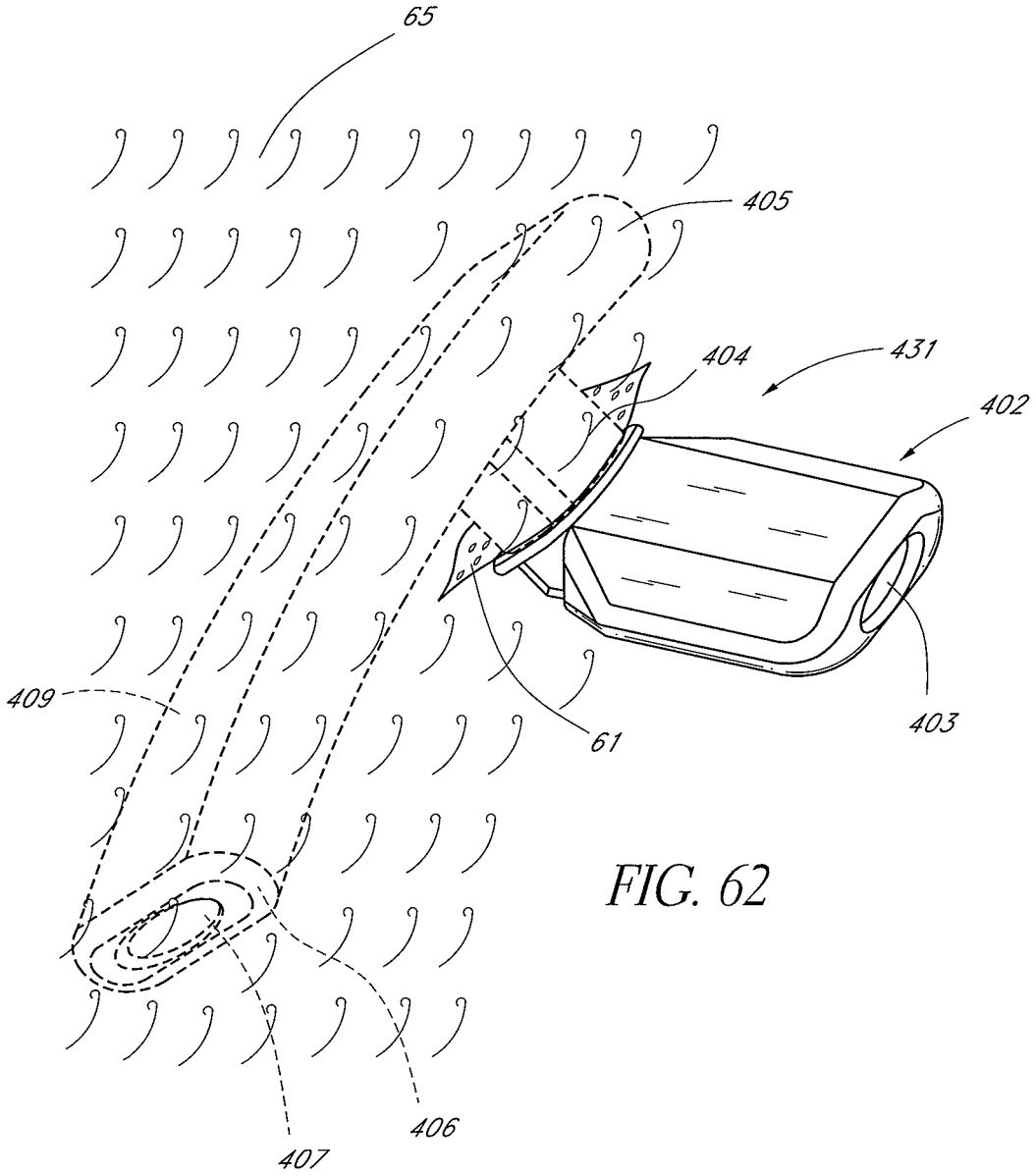

FIG. 62

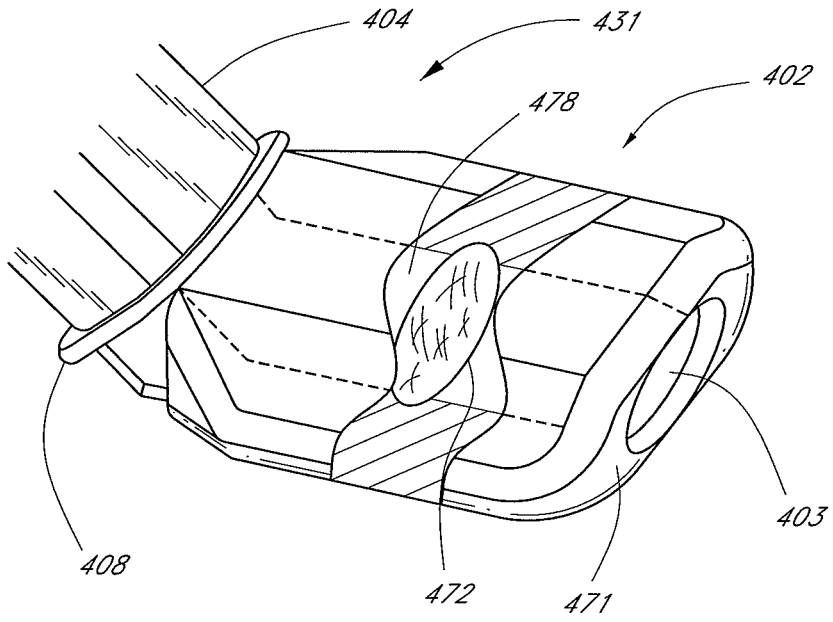

FIG. 63

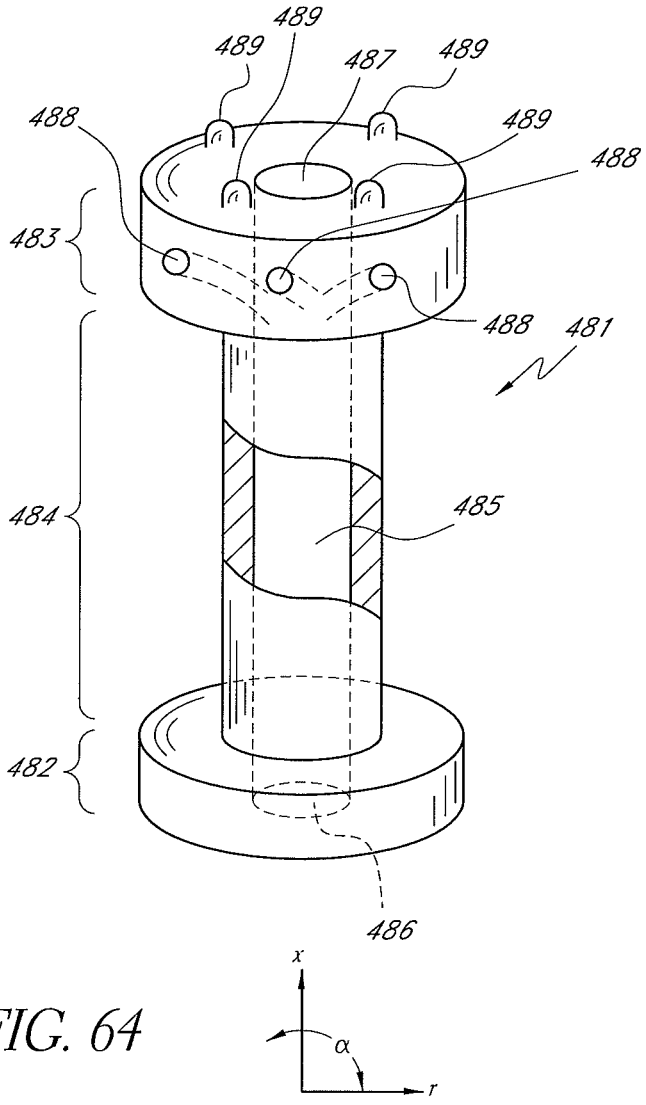

FIG. 64

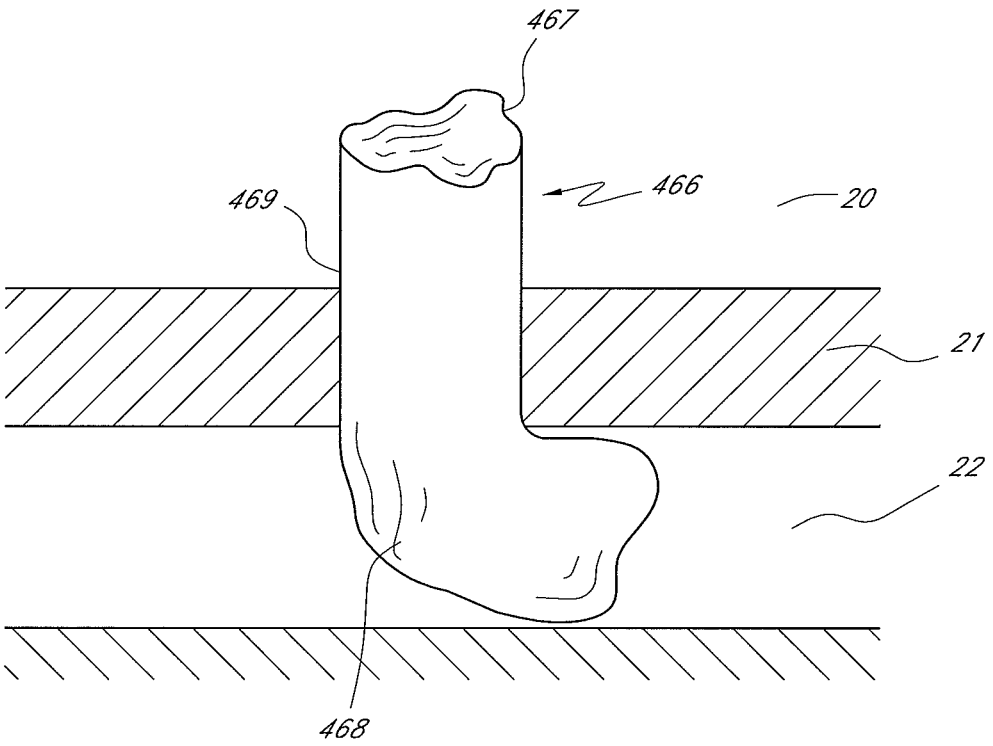

FIG. 65

OCULAR IMPLANT WITH THERAPEUTIC AGENTS AND METHODS THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of U.S. patent application Ser. No. 12/772,889, filed May 3, 2010, now U.S. Pat. No. 8,348,877 B2, issued Jan. 18, 2013, entitled "Ocular Implant With Therapeutic Agents And Methods Thereof," which is a continuation application of U.S. patent application Ser. No. 10/706,300, filed Nov. 12, 2003 (the "Ser. No. 10/706,300 application"), now U.S. Pat. No. 7,708,711 B2, issued May 4, 2010, entitled "Ocular Implant With Therapeutic Agents And Methods Thereof," which is a continuation-in-part of U.S. patent application Ser. No. 10/395,633, filed Mar. 21, 2003, now abandoned, entitled "Stent With Drug Coating," which is a continuation application of U.S. patent application Ser. No. 09/549,350, filed Apr. 14, 2000, now U.S. Pat. No. 6,638,239 B1, issued Oct. 28, 2003, entitled "Apparatus And Method For Treating Glaucoma."

The Ser. No. 10/706,300 application is also a continuation-in-part of U.S. patent application Ser. No. 10/634,213, filed Aug. 5, 2003, now U.S. Pat. No. 7,867,186 B2, issued Jan. 11, 2011, entitled "Devices And Methods For Treatment of Ocular Disorders," which is a continuation-in-part of U.S. patent application Ser. No. 10/118,578, filed Apr. 8, 2002, now U.S. Pat. No. 7,135,009 B2, issued Nov. 14, 2006, entitled "Glaucoma Stent And Methods Thereof For Glaucoma Treatment," which claims the priority benefit of U.S. Provisional Application No. 60/281,973, filed Apr. 7, 2001. The aforementioned U.S. patent application Ser. No. 10/634,213 also claims the priority benefits of U.S. Provisional Application No. 60/401,166, filed Aug. 5, 2002, and U.S. Provisional Application No. 60/451,226, filed Feb. 28, 2003.

The Ser. No. 10/706,300 application is also a continuation-in-part of U.S. patent application Ser. No. 10/046,137, filed Nov. 8, 2001, now abandoned, entitled "Drug-Releasing Trabecular Implant for Glaucoma Treatment," which claims the priority benefit of U.S. Provisional Application No. 60/281,247, filed Apr. 3, 2001.

The Ser. No. 10/706,300 application also claims the priority benefits of U.S. Provisional Patent Application No. 60/425,911, filed Nov. 12, 2002, and U.S. Provisional Patent Application No. 60/431,918, filed Dec. 9, 2002.

This application claims priority to all of the aforementioned priority documents, the entireties of all of which are hereby incorporated by reference herein.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present application relates generally to medical devices and methods for reducing the intraocular pressure in an animal eye and, more particularly, to shunt-type stenting devices for permitting and/or enhancing aqueous outflow from the eye's anterior chamber toward existing outflow pathways and associated methods thereof for the treatment of glaucoma in general. Furthermore, the invention relates to the delivery of bioactive agents to ocular tissue from an implant.

2. Description of the Related Art

The human eye is a specialized sensory organ capable of light reception and able to receive visual images. The trabecular meshwork serves as a drainage channel and is located in the anterior chamber angle formed between the iris and the cornea. The trabecular meshwork maintains a balanced pressure in the anterior chamber of the eye by allowing aqueous humor to flow from the anterior chamber.

About two percent of people in the United States have glaucoma. Glaucoma is a group of eye diseases encompassing a broad spectrum of clinical presentations, etiologies, and treatment modalities. Glaucoma causes pathological changes in the optic nerve, visible on the optic disk, and it causes corresponding visual field loss, resulting in blindness if untreated. Lowering intraocular pressure is a major treatment goal in all glaucomas.

In glaucomas associated with an elevation in eye pressure (intraocular hypertension), the source of resistance to outflow of aqueous humor is mainly in the trabecular meshwork. The tissue of the trabecular meshwork allows the aqueous humor ("aqueous") to enter Schlemm's canal, which then empties into aqueous collector channels in the posterior wall of Schlemm's canal and then into aqueous veins, which form the episcleral venous system. Aqueous humor is a transparent liquid that fills the region between the cornea, at the front of the eye, and the lens. The aqueous humor is continuously secreted by the ciliary body around the lens, so there is an essentially constant flow of aqueous humor from the ciliary body to the eye's anterior chamber. The anterior chamber pressure is determined by a balance between the production of aqueous and its exit through the trabecular meshwork (major route) or uveal scleral outflow (minor route). The trabecular meshwork is located between the outer rim of the iris and the back of the cornea, in the anterior chamber angle. The portion of the trabecular meshwork adjacent to Schlemm's canal (the juxtacanalicular meshwork) causes most of the resistance to aqueous outflow.

Glaucoma is grossly classified into two categories: closed-angle glaucoma, also known as "angle closure" glaucoma, and open-angle glaucoma. Closed-angle glaucoma is caused by closure of the anterior chamber angle by contact between the iris and the inner surface of the trabecular meshwork. Closure of this anatomical angle prevents normal drainage of aqueous humor from the anterior chamber of the eye.

Open-angle glaucoma is any glaucoma in which the angle of the anterior chamber remains open, but the exit of aqueous through the trabecular meshwork is diminished. The exact cause for diminished filtration is unknown for most cases of open-angle glaucoma. Primary open-angle glaucoma is the most common of the glaucomas, and it is often asymptomatic in the early to moderately advanced stage. Patients may suffer substantial, irreversible vision loss prior to diagnosis and treatment. However, there are secondary open-angle glaucomas that may include edema or swelling of the trabecular spaces (e.g., from corticosteroid use), abnormal pigment dispersion, or diseases such as hyperthyroidism that produce vascular congestion.

Current therapies for glaucoma are directed at decreasing intraocular pressure. Medical therapy includes topical ophthalmic drops or oral medications that reduce the production or increase the outflow of aqueous. However, these drug therapies for glaucoma are sometimes associated with significant side effects, such as headache, blurred vision, allergic reactions, death from cardiopulmonary complications, and potential interactions with other drugs. When drug therapy fails, surgical therapy is used. Surgical therapy for open-angle glaucoma consists of laser trabeculoplasty, trabeculectomy, and implantation of aqueous shunts after failure of trabeculectomy or if trabeculectomy is unlikely to succeed. Trabeculectomy is a major surgery that is widely used and is augmented with topically applied anticancer drugs, such as 5-fluorouracil or mitomycin-C to decrease scarring and increase the likelihood of surgical success.

Approximately 100,000 trabeculectomies are performed on Medicare-age patients per year in the United States. This number would likely increase if the morbidity associated with trabeculectomy could be decreased. The current morbidity associated with trabeculectomy consists of failure (10-15%); infection (a life long risk of 2-5%); choroidal hemorrhage, a severe internal hemorrhage from low intraocular pressure, resulting in visual loss (1%); cataract formation; and hypotony maculopathy (potentially reversible visual loss from low intraocular pressure).

For these reasons, surgeons have tried for decades to develop a workable surgery for the trabecular meshwork.

The surgical techniques that have been tried and practiced are goniotomy/trabeculotomy and other mechanical disruptions of the trabecular meshwork, such as trabeculopuncture, goniophotoablation, laser trabecular ablation, and goniocurretage. These are all major operations and are briefly described below.

Goniotomy/Trabeculotomy:

Goniotomy and trabeculotomy are simple and directed techniques of microsurgical dissection with mechanical disruption of the trabecular meshwork. These initially had early favorable responses in the treatment of open-angle glaucoma. However, long-term review of surgical results showed only limited success in adults. In retrospect, these procedures probably failed due to cellular repair and fibrosis mechanisms and a process of "filling in." Filling in is a detrimental effect of collapsing and closing in of the opening created in the trabecular meshwork. Once the openings close, the pressure builds back up and the surgery fails.

Trabeculopuncture:

Q-switched Neodymium (Nd) YAG lasers also have been investigated as an optically invasive technique for creating full-thickness holes in trabecular meshwork. However, the relatively small hole created by this trabeculopuncture technique exhibits a filling-in effect and fails.

Goniophotoablation/Laser Trabecular Ablation:

Goniophotoablation is disclosed by Berlin in U.S. Pat. No. 4,846,172 and involves the use of an excimer laser to treat glaucoma by ablating the trabecular meshwork. This was demonstrated not to succeed by clinical trial. Hill et al. disclosed the use of an Erbium:YAG laser to create full-thickness holes through trabecular meshwork (Hill et al., Lasers in Surgery and Medicine 11:341-346, 1991). This technique was investigated in a primate model and a limited human clinical trial at the University of California, Irvine. Although morbidity was zero in both trials, success rates did not warrant further human trials. Failure was again from filling in of surgically created defects in the trabecular meshwork by repair mechanisms. Neither of these is a viable surgical technique for the treatment of glaucoma.

Goniocurretage:

This is an ab interno (from the inside), mechanically disruptive technique that uses an instrument similar to a cyclodialysis spatula with a microcurette at the tip. Initial results were similar to trabeculotomy: it failed due to repair mechanisms and a process of filling in.

Although trabeculectomy is the most commonly performed filtering surgery, viscocanalostomy (VC) and non penetrating trabeculectomy (NPT) are two new variations of filtering surgery. These are ab externo (from the outside), major ocular procedures in which Schlemm's canal is surgically exposed by making a large and very deep scleral flap. In the VC procedure, Schlemm's canal is cannulated and viscoelastic substance injected (which dilates Schlemm's canal and the aqueous collector channels). In the NPT procedure, the inner wall of Schlemm's canal is stripped off after surgically exposing the canal.

Trabeculectomy, VC, and NPT involve the formation of an opening or hole under the conjunctiva and scleral flap into the anterior chamber, such that aqueous humor is drained onto the surface of the eye or into the tissues located within the lateral wall of the eye. These surgical operations are major procedures with significant ocular morbidity. Where trabeculectomy, VC, and NPT were thought to have a low chance for success in particular cases, a number of implantable drainage devices have been used to ensure that the desired filtration and outflow of aqueous humor through the surgical opening will continue. The risk of placing a glaucoma drainage device also includes hemorrhage, infection, and diplopia (double vision).

All of the above surgeries and variations thereof have numerous disadvantages and moderate success rates. They involve substantial trauma to the eye and require great surgical skill in creating a hole through the full thickness of the sclera into the subconjunctival space. The procedures are generally performed in an operating room and have a prolonged recovery time for vision.

The complications of existing filtration surgery have prompted ophthalmic surgeons to find other approaches to lowering intraocular pressure or treating tissue of trabecular meshwork.

The trabecular meshwork and juxtacanalicular tissue together provide the majority of resistance to the outflow of aqueous and, as such, are logical targets for tissue stimulation/rejuvenating or shunting in the treatment of open-angle glaucoma. In addition, minimal amounts of tissue are displaced and functions of the existing physiologic outflow pathways are restored.

As reported in Arch. Ophthalm. (2000) 118:412, glaucoma remains a leading cause of blindness, and filtration surgery remains an effective, important option in controlling the disease. However, modifying existing filtering surgery techniques in any profound way to increase their effectiveness appears to have reached a dead end. The article further states that the time has come to search for new surgical approaches that may provide better and safer care for patients with glaucoma.

Examples of implantable shunts and surgical methods for maintaining an opening for the release of aqueous from the anterior chamber of the eye to the sclera or space beneath the conjunctiva have been disclosed in, for example, Hsia et al., U.S. Pat. No. 6,059,772 and Baerveldt, U.S. Pat. No. 6,050,970.

Examples of implantable shunts or devices for maintaining an opening for the release of aqueous humor from the anterior chamber of the eye to the sclera or space underneath conjunctiva have been disclosed in U.S. Pat. No. 6,007,511 (Prywes), U.S. Pat. No. 6,007,510 (Nigam), U.S. Pat. No. 5,893,837 (Eagles et al.), U.S. Pat. No. 5,882,327 (Jacob), U.S. Pat. No. 5,879,319 (Pynson et al.), U.S. Pat. No. 5,807,302 (Wandel), U.S. Pat. No. 5,752,928 (de Roulhac et al.), U.S. Pat. No. 5,743,868 (Brown et al.), U.S. Pat. No. 5,704,907 (Nordquist et al.), U.S. Pat. No. 5,626,559 (Solomon), U.S. Pat. No. 5,626,558 (Suson), U.S. Pat. No. 5,601,094 (Reiss), RE. 35,390 (Smith), U.S. Pat. No. 5,558,630 (Fisher), U.S. Pat. No. 5,558,629 (Baerveldt et al.), U.S. Pat. No. 5,520,631 (Nordquist et al.), U.S. Pat. No. 5,476,445 (Baerveldt et al.), U.S. Pat. No. 5,454,796 (Krupin), U.S. Pat. No. 5,433,701 (Rubinstein), U.S. Pat. No. 5,397,300 (Baerveldt et al.), U.S. Pat. No. 5,372,577 (Ungerleider), U.S. Pat. No. 5,370,607 (Memmen), U.S. Pat. No. 5,338,291 (Speckman et al.), U.S. Pat. No. 5,300,020 (L'Esperance, Jr.), U.S. Pat. No. 5,178,

604 (Baerveldt et al.), U.S. Pat. No. 5,171,213 (Price, Jr.), U.S. Pat. No. 5,041,081 (Odrich), U.S. Pat. No. 4,968,296 (Ritch et al.), U.S. Pat. No. 4,936,825 (Ungerleider), U.S. Pat. No. 4,886,488 (White), U.S. Pat. No. 4,750,901 (Molteno), U.S. Pat. No. 4,634,418 (Binder), U.S. Pat. No. 4,604,087 (Joseph), U.S. Pat. No. 4,554,918 (White), U.S. Pat. No. 4,521,210 (Wong), U.S. Pat. No. 4,428,746 (Mendez), U.S. Pat. No. 4,402,681 (Haas et al.), U.S. Pat. No. 4,175,563 (Arenberg et al.), and U.S. Pat. No. 4,037,604 (Newkirk).

All of the above embodiments and variations thereof have numerous disadvantages and moderate success rates. They involve substantial trauma to the eye and require great surgical skill in creating a hole through the full thickness of the sclera into the subconjunctival space. The procedures are generally performed in an operating room and involve a prolonged recovery time for vision. The complications of existing filtration surgery have prompted ophthalmic surgeons to find other approaches to lowering intraocular pressure.

Because the trabecular meshwork and juxtacanalicular tissue together provide the majority of resistance to the outflow of aqueous, they are logical targets for surgical removal in the treatment of open-angle glaucoma. In addition, minimal amounts of tissue need be altered and existing physiologic outflow pathways can be utilized.

SUMMARY OF THE INVENTION

What is needed, therefore, is an extended, site-specific treatment method for glaucoma that is faster, safer, and less expensive than currently available modalities. There is a great clinical need for an improved method of treating glaucoma that is faster, safer, and less expensive than currently available drug or surgical modalities. The methods disclosed herein include ab intern and ab externo procedures that involve non-flap operations. The method herein may further comprise using an innovative stenting device.

In accordance with some embodiments, a method of treating an ocular disorder is provided. The method involves introducing an implant into an anterior chamber of an eye. The implant is implanted into eye tissue adjacent the anterior chamber such that a proximal end of the implant resides in the anterior chamber following implantation. A therapeutic agent is eluted from the implant into the eye. Desirably, the release of the therapeutic agent from the implant is controlled. The controlled release of the therapeutic agent can be at a chosen rate and/or for a selected duration which can be episodic or periodic. The therapeutic agent can be an antiproliferative agent, an anti-inflammatory drug, or a compound for treating glaucoma or ocular hypertension.

In some preferred embodiments, the seton has an inlet portion configured to extend through a portion of the trabecular meshwork of an eye, and an outlet portion configured to extend into Schlemm's canal of the eye, wherein the inlet portion is disposed at an angle relative to the outlet portion. In some embodiments, the outlet portion has a lumen with an oval cross-section having a long axis.

The outlet portion in certain embodiments has a longitudinal axis, such that the long axis of the oval cross-section and the longitudinal axis of the outlet portion define a plane, the inlet portion having a longitudinal axis that lies outside the plane at an angle θ (theta) thereto.

In some preferred arrangements, the seton comprises an inlet portion, configured to extend through a portion of the trabecular meshwork; an outlet portion, configured to extend into Schlemm's canal; and at least one protrusion on the outlet portion, configured to exert traction against an inner surface of Schlemm's canal. This protrusion can comprise at least one barb or ridge.

Some preferred embodiments comprise an inlet portion configured to extend through a portion of the trabecular meshwork, an outlet portion configured to extend into Schlemm's canal, and a one-way valve within the inlet and/or outlet portions.

A method for delivering a seton within an eye is disclosed, comprising providing an elongate guide member, advancing a distal end of the guide member through at least a portion of the trabecular meshwork of the eye, advancing the seton along the guide member toward the distal end, and positioning the seton to conduct aqueous humor between the anterior chamber of the eye and Schlemm's canal.

In certain embodiments, the advancing of the guide member comprises advancing it from the anterior chamber into the trabecular meshwork. In further embodiments, the positioning comprises positioning an end of the seton within Schlemm's canal adjacent to an aqueous collection channel.

Certain preferred embodiments include an apparatus for delivering a seton to the anterior chamber of an eye comprising an elongate tube having a lumen, an outer surface, and a distal end; a removable, elongate guide member within the lumen, configured to permit the seton to be advanced and to be positioned in the trabecular meshwork of the eye. This apparatus can further comprise a cutting member positioned at the distal end of the tube. The cutting member can be selected from the group consisting of a knife, a laser probe, a pointed guide member, a sharpened distal end of said tube, and an ultrasonic cutter. The apparatus can also further comprise an opening in the outer surface of the tube, configured to allow fluid infusion into the eye.

In further preferred embodiments, an apparatus for delivering a seton in an eye, comprises an elongate member adapted for insertion into an anterior chamber of the eye, the elongate member having a distal end portion configured to retain the seton therein, the distal end portion comprising a cutting member configured to form an opening in the trabecular meshwork of the eye for receipt of the seton, such that one end of the seton is in Schlemm's canal. The elongate member can further comprise a lumen that conducts fluid toward said distal end portion.

The preferred embodiment provides further surgical treatment of glaucoma (trabecular bypass surgery) at the level of trabecular meshwork and restores existing physiological outflow pathways. An implant bypasses diseased trabecular meshwork at the level of trabecular meshwork and which restores existing physiological outflow pathways. The implant has an inlet end, an outlet end and a lumen therebetween. The inlet is positioned in the anterior chamber at the level of the internal trabecular meshwork and the outlet end is positioned at about the exterior surface of the diseased trabecular meshwork and/or into fluid collection channels of the existing outflow pathways.

In accordance with a preferred method, trabecular bypass surgery creates an opening or a hole through the diseased trabecular meshwork through minor microsurgery. To prevent "filling in" of the hole, a biocompatible elongated implant is placed within the hole as a seton, which may include, for example, a solid rod or hollow tube. In one exemplary embodiment, the seton implant may be positioned across the diseased trabecular meshwork alone and it does not extend into the eye wall or sclera. In another embodiment, the inlet end of the implant is exposed to the anterior chamber of the eye while the outlet end is positioned at the exterior surface of the trabecular meshwork. In another exemplary

embodiment, the outlet end is positioned at and over the exterior surface of the trabecular meshwork and into the fluid collection channels of the existing outflow pathways. In still another embodiment, the outlet end is positioned in the Schlemm's canal. In an alternative embodiment, the outlet end enters into fluid collection channels up to the level of the aqueous veins with the seton inserted in a retrograde or antegrade fashion.

According to the preferred embodiment, the seton implant is made of biocompatible material, which is either hollow to allow the flow of aqueous humor or solid biocompatible material that imbibes aqueous. The material for the seton may be selected from the group consisting of porous material, semi-rigid material, soft material, hydrophilic material, hydrophobic material, hydrogel, elastic material, and the like.

In further accordance with the preferred embodiment, the seton implant may be rigid or it may be made of relatively soft material and is somewhat curved at its distal section to fit into the existing physiological outflow pathways, such as Schlemm's canal. The distal section inside the outflow pathways may have an oval shape to stabilize the seton in place without undue suturing. Stabilization or retention of the seton may be further strengthened by a taper end and/or by at least one ridge or rib on the exterior surface of the distal section of the seton, or other surface alterations designed to retain the seton.

In one embodiment, the seton may include a micropump, one-way valve, or semi-permeable membrane if reflux of red blood cells or serum protein becomes a clinical problem. It may also be useful to use a biocompatible material that hydrates and expands after implantation so that the seton is locked into position around the trabecular meshwork opening or around the distal section of the seton.

One of the advantages of trabecular bypass surgery, as disclosed herein, and the use of a seton implant to bypass diseased trabecular meshwork at the level of trabecular meshwork and thereby use existing outflow pathways is that the treatment of glaucoma is substantially simpler than in existing therapies. A further advantage of the invention is the utilization of simple microsurgery that may be performed on an outpatient basis with rapid visual recovery and greatly decreased morbidity. Finally, a distinctly different approach is used than is found in existing implants. Physiological outflow mechanisms are used or re-established by the implant of the present invention, in contradistinction with previously disclosed methodologies.

A device and method are provided for improved treatment of intraocular pressure due to glaucoma. A trabecular shunting and stenting device is adapted for implantation within a trabecular meshwork of an eye such that aqueous humor flows controllably from an anterior chamber of the eye to Schlemm's canal, bypassing the trabecular meshwork. The trabecular stenting device comprises a quantity of bioactive agents effective in treating glaucoma, which are controllably released from the device into cells of the trabecular meshwork and/or Schlemm's canal. Depending upon the specific treatment contemplated, bioactive agents may be utilized in conjunction with the trabecular stenting device such that aqueous flow either increases or decreases as desired. Placement of the trabecular stenting device within the eye and incorporation, and eventual release, of a proven bioactive agents glaucoma therapy will reduce, inhibit or slow the effects of glaucoma.

One aspect of the invention provides a trabecular stenting device that is implantable within an eye. The device comprises an inlet section containing at least one lumen, an outlet section having at least one outlet end. In one embodiment, there provides a flow-restricting member within the lumen that is configured to prevent at least one component of blood from passing through the flow-restricting member. In another embodiment, the device further comprises a middle section having at least one lumen. The middle section is fixedly attached between the inlet section and the outlet section and the lumen is in fluid communication with the lumens of the inlet and outlet sections. The device is configured to permit fluid entering the lumens of the inlet section, the middle section, and the outlet section, and then exit the outlet section through the at least one outlet end.

Another aspect of the invention provides a method of treating glaucoma. The method comprises providing at least one bioactive agent or substance incorporated into a trabecular stenting device, implanting the trabecular stenting device within a trabecular meshwork of an eye such that a first end of the trabecular stent is positioned in an anterior chamber of the eye while a second end is positioned in a Schlemm's canal, and allowing the stenting device to release a quantity of the bioactive agent into the eye. The first and second ends of the trabecular stenting device establish a fluid communication between the anterior chamber and the Schlemm's canal.

In another aspect of the invention, the bioactive agent comprises genes, growth factors, TGF-beta, scar inhibitors, and the like.

Still another aspect of the invention provides a method of regulating intraocular pressure within an eye. The method comprises: providing at least one bioactive agent incorporated into a trabecular stenting device; implanting the trabecular stenting device within a trabecular meshwork of an eye such that a first end of the trabecular stent is positioned in an anterior chamber of the eye while a second end is positioned in a Schlemm's canal, wherein the first and second ends of the trabecular stenting device establish a fluid communication between the anterior chamber and the Schlemm's canal; and allowing the stenting device to release a quantity of said bioactive agent into the eye.

Another aspect of the invention provides an apparatus for implanting a trabecular shunting/stenting device within an eye. The apparatus comprises a syringe portion and a cannula portion that has proximal and distal ends. The proximal end of the cannula portion is attached to the syringe portion. The cannula portion further comprises a first lumen and at least one irrigating hole disposed between the proximal and distal ends of the cannula portion. The irrigating hole is in fluid communication with the lumen. The apparatus further includes a holder comprising a second lumen for holding the trabecular stenting device. A distal end of the second lumen opens to the distal end of the cannula portion, and a proximal end of the second lumen is separated from the first lumen of the cannula portion. The holder holds the trabecular stenting device during implantation of the device within the eye, and the holder releases the trabecular stenting device when a practitioner activates deployment of the device.

Another aspect of the invention provides a method of implanting a trabecular stenting device within an eye. The method comprises creating a first incision in a cornea on a first side of the eye, wherein the first incision passes through the cornea into an anterior chamber of the eye. The method further comprises passing an incising device through the first incision and moving a distal end of the incising device across the anterior chamber to a trabecular meshwork residing on a second side of the eye, and using the incising device to create a second incision. The second incision is in the trabecular meshwork, passing from the anterior chamber through the trabecular meshwork into a Schlemm's canal. The method further comprises inserting the trabecular shunting/stenting device into a distal space of a delivery applicator. The method

further comprises advancing the cannula portion having the trabecular stenting device through the first incision, across the anterior chamber and into the second incision, wherein an outlet section of the trabecular stenting device is implanted into Schlemm's canal while an inlet section of the trabecular stenting device remains in fluid communication with the anterior chamber. The method still further comprises releasing the trabecular stenting device from the holder of the delivery applicator.

The trabecular meshwork and juxtacanalicular tissue together provide the majority of resistance to the outflow of aqueous and, as such, are logical targets for the treatment of glaucoma. Various embodiments of glaucoma devices and methods are disclosed herein for treating glaucoma by an ab intern procedure or an ab externo procedure, with respect to trabecular meshwork. The "ab interno" procedure is herein intended to mean any procedure that creates an opening from the anterior chamber through trabecular meshwork outwardly toward Schlemm's canal or toward scleral/cornea wall. This ab interno procedure may be initiated through the scleral wall or cornea wall into the anterior chamber as a first step. The "ab externo" procedure is herein intended to mean any procedure that creates an opening on the scleral wall through trabecular meshwork inwardly toward the anterior chamber. In most "ab externo" procedures disclosed herein, an instrument is passed through or contacts Schlemm's canal before entering trabecular meshwork and approaching the anterior chamber. The trabecular meshwork can generally be said to be bordered on one side by the anterior chamber and on the other side by Schlemm's canal.

Glaucoma surgical morbidity would greatly decrease if one were to bypass the focal resistance to outflow of aqueous only at the point of resistance, and to utilize remaining, healthy aqueous outflow mechanisms. This is in part because episcleral aqueous humor exerts a backpressure that prevents intraocular pressure from falling too low, and one could thereby avoid hypotony. Thus, such a surgery would virtually eliminate the risk of hypotony-related maculopathy and choroidal hemorrhage. Furthermore, visual recovery would be very rapid, and the risk of infection would be very small, reflecting a reduction in incidence from 2-5% to about 0.05%.

Copending U.S. application Ser. No. 09/549,350, filed Apr. 14, 2000, entitled APPARATUS AND METHOD FOR TREATING GLAUCOMA, and copending U.S. application Ser. No. 09/704,276, filed Nov. 1, 2000, entitled GLAUCOMA TREATMENT DEVICE, disclose devices and methods of placing a trabecular shunt ab interno, i.e., from inside the anterior chamber through the trabecular meshwork, into Schlemm's canal. The entire contents of each one of these copending patent applications are hereby incorporated by reference herein. This application encompasses both ab interno and ab externo glaucoma shunts or stents and methods thereof.

One technique performed in accordance with certain aspects herein can be referred to generally as "trabecular bypass surgery." Advantages of this type of surgery include lowering intraocular pressure in a manner that is simple, effective, disease site-specific, and can potentially be performed on an outpatient basis.

Generally, trabecular bypass surgery (TBS) creates an opening, a slit, or a hole through trabecular meshwork with minor microsurgery. TBS has the advantage of a much lower risk of choroidal hemorrhage and infection than prior techniques, and it uses existing physiologic outflow mechanisms. In some aspects, this surgery can potentially be performed under topical or local anesthesia on an outpatient basis with rapid visual recovery. To prevent "filling in" of the hole, a biocompatible elongated hollow device is placed within the hole and serves as a stent. U.S. patent application Ser. No. 09/549,350, filed Apr. 14, 2000 and the corresponding WO PCT US 01/07398 filed Mar. 8, 2001, the entire contents of which are hereby incorporated by reference herein, disclose trabecular bypass surgery in details.

As described in U.S. patent application Ser. No. 09/549,350, filed Apr. 14, 2000, and U.S. application Ser. No. 09/704,276, filed Nov. 1, 2000, a trabecular shunt or stent for transporting aqueous humor is provided. The trabecular stent includes a hollow, elongate tubular element, having an inlet section and an outlet section. The outlet section may optionally include two segments or elements, adapted to be positioned and stabilized inside Schlemm's canal. In one embodiment, the device appears as a "T" or an "L" shaped device.

In accordance with one aspect of at least one of the inventions disclosed herein, a delivery apparatus (or "applicator") is used for placing a trabecular stent through a trabecular meshwork of an eye. Certain embodiments of such a delivery apparatus are disclosed in copending U.S. application Ser. No. 10/101,548, filed Mar. 18, 2002, entitled APPLICATOR AND METHODS FOR PLACING A TRABECULAR SHUNT FOR GLAUCOMA TREATMENT, and U.S. Provisional Application No. 60/276,609, filed Mar. 16, 2001, entitled APPLICATOR AND METHODS FOR PLACING A TRABECULAR SHUNT FOR GLAUCOMA TREATMENT, the entire contents of each one of which are hereby incorporated by reference herein.

The stent has an inlet section and an outlet section. The delivery apparatus includes a handpiece, an elongate tip, a holder and an actuator. The handpiece has a distal end and a proximal end. The elongate tip is connected to the distal end of the handpiece. The elongate tip has a distal portion and is configured to be placed through a corneal incision and into an anterior chamber of the eye. The holder is attached to the distal portion of the elongate tip. The holder is configured to hold and release the inlet section of the trabecular stent. The actuator is on the handpiece and actuates the holder to release the inlet section of the trabecular stent from the holder. When the trabecular stent is deployed from the delivery apparatus into the eye, the outlet section is positioned in substantially opposite directions inside Schlemm's canal. In one embodiment, a deployment mechanism within the delivery apparatus includes a push-pull type plunger.

Some aspects of at least one of the inventions disclosed herein relate to devices for reducing intraocular pressure by providing outflow of aqueous from an anterior chamber of an eye. The device generally comprises an elongated tubular member and cutting means. The tubular member is adapted for extending through a trabecular meshwork of the eye. The tubular member generally comprises a lumen having an inlet port and at least one outlet port for providing a flow pathway. The cutting means is mechanically connected to or is an integral part of the tubular member for creating an incision in the trabecular meshwork for receiving at least a portion of the tubular member.

In one embodiment, a self-trephining glaucoma stent is provided for reducing and/or balancing intraocular pressure in an eye. The stent generally comprises a snorkel and a curved blade. The snorkel generally comprises an upper seat for stabilizing said stent within the eye, a shank and a lumen. The shank is mechanically connected to the seat and is adapted for extending through a trabecular meshwork of the eye. The lumen extends through the snorkel and has at least one inlet flow port and at least one outlet flow port. The blade is mechanically connected to the snorkel. The blade generally

comprises a cutting tip proximate a distal-most point of the blade for making an incision in the trabecular meshwork for receiving the shank.

Some aspects of at least one of the inventions disclosed herein relate to methods of implanting a trabecular stent device in an eye. In one embodiment, the device has a snorkel mechanically connected to a blade. The blade is advanced through a trabecular meshwork of the eye to cut the trabecular meshwork and form an incision therein. At least a portion of the snorkel is inserted in the incision to implant the device in the eye.

Some aspects provide a self-trephining glaucoma stent and methods thereof, which advantageously allow for a "one-step" procedure in which the incision and placement of the stent are accomplished by a single device and operation. This desirably allows for a faster, safer, and less expensive surgical procedure. In any of the embodiments, fiducial markings, indicia, or the like and/or positioning of the stent device in a preloaded applicator may be used for proper orientation and alignment of the device during implantation.

Among the advantages of trabecular bypass surgery is its simplicity. The microsurgery may potentially be performed on an outpatient basis with rapid visual recovery and greatly decreased morbidity. There is a lower risk of infection and choroidal hemorrhage, and there is a faster recovery, than with previous techniques.

Some aspects of at least one of the inventions disclosed herein relate to a medical device system for treating glaucoma of an eye comprising using OCT (optical coherence tomography) as an imaging and locating system for trabecular stent placement. In one embodiment, the procedure would first be set up with triangulation or some means to reliably establish the implant location in x, y, and z coordinates by using OCT within a few microns, most preferably in a non-invasive, non-contact manner. Having acquired the target space or location, the trabecular stent device would then be injected into place either via an ab intern procedure or an ab externo procedure. An article by Hoerauf et al. (Graefe's Arch Clin Exp Ophthalmol 2000; 238:8-18 published by Springer-Verlag), entire contents of which are incorporated herein by reference, discloses a slit-lamp adapted optical coherence tomography of the anterior segment.

Some aspects of at least one of the inventions disclosed herein relate to a 'foldable' stent wherein the size of the stent is reduced in order to place it through a yet smaller ocular entrance wound, as small as half or less than the size of the unfolded stent. The smallest size wound is important to aid in recovery, to prevent complications, and to minimize the preparation and extent of the surgical environment. In another embodiment, the device is positioned through the trabecular meshwork in an ab externo or ab interno procedure. Reliable visualization (OCT, UBM, gonioscope, electromagnetic or other means) is a key enabler for micro precision surgery such as a trabecular bypass surgery using a microstent.

Some aspects of at least one of the inventions disclosed herein relate to a medical device system with trephining capability, wherein a cutting mechanism is on or as part of the applicator for purposes of making the hole in trabecular meshwork for stent insertion. In one aspect, a cutting tip may protrude through the lumen of the stent. In another, the tip extends down the side of the snorkel without entering the lumen. In still another, the tip either passes through the lumen or down the side and further extends to the tip of the stent that is the leading edge during insertion. In one embodiment, the cutting tip can be designed to retract after making the incision but before insertion of the stent into Schlemm's canal if it interferes with the insertion operation. It could also be retracted after insertion of the stent into Schlemm's canal.

Some aspects of at least one of the inventions disclosed herein provide an implant for treating glaucoma, the implant having a longitudinal implant axis, and comprising an outflow portion through which a portion of the longitudinal implant axis passes, the outflow portion shaped and sized to be (a) introduced into Schlemm's canal with the portion of the longitudinal implant axis at an angle to Schlemm's canal; and (b) received with Schlemm's canal regardless of the rotational orientation of the outflow portion about the portion of the longitudinal implant axis during the introduction; and an inflow portion in fluid communication with the outflow portion, the inflow portion configured to permit communication of fluid from the anterior chamber of the eye to the outflow portion.

Some aspects of at least one of the inventions disclosed herein provide an implant for treating glaucoma, comprising: an outflow portion, sized and shaped to be received within Schlemm's canal, the outflow portion comprising: an outflow portion base having an outflow opening and at least one standoff member disposed to space the outflow opening from a wall of Schlemm's canal, such that the opening is unobstructed by the canal wall.

Some aspects of at least one of the inventions disclosed herein provide an implant for treating glaucoma, the implant having a longitudinal implant axis and comprising: a first portion at a first end of the longitudinal implant axis, the first portion sized and configured to reside in Schlemm's canal, such that the first portion has a maximum dimension along a longitudinal axis of Schlemm's canal that is not substantially greater than a dimension of the first portion that runs perpendicular to both the longitudinal axis of Schlemm's canal and to the longitudinal implant axis; and a second portion at a second end of the longitudinal implant axis, the second portion configured to provide fluid communication between the anterior chamber and the first portion.

Some aspects of at least one of the inventions disclosed herein provide an implant for treating glaucoma, comprising: an outflow portion, sized and shaped to be received within Schlemm's canal; an inflow portion in fluid communication with the outflow portion, the inflow portion configured to be disposed in the anterior chamber of the eye; and a central portion extending between the inflow and outflow portions; the outflow portion having a diameter that is no more than three times the diameter of the central portion.

In accordance with one embodiment of at least one of the inventions disclosed herein, an implant for treating glaucoma is provided. The implant includes a longitudinal implant axis, and comprises an outflow portion through which said longitudinal implant axis passes. The outflow portion is shaped and sized to be introduced into Schlemm's canal with the portion of the longitudinal implant axis at an angle to Schlemm's canal. The outflow portion is also shaped and sized to be received within Schlemm's canal regardless of a rotational orientation of the outflow portion about said longitudinal implant axis during said introduction. The implant also comprises an inflow portion configured to permit communication of fluid from the anterior chamber of the eye to the outflow portion.

In accordance with another embodiment of at least one of the inventions disclosed herein, an implant for treating glaucoma is provided. The implant comprises an outflow portion, sized and shaped to be received within Schlemm's canal. The outflow portion comprises an outflow portion base having an outflow opening and at least one standoff member disposed to

space said outflow opening from a wall of Schlemm's canal, such that said outflow opening is unobstructed by said canal wall.

In accordance with a further embodiment of at least one of the inventions disclosed herein, an implant for treating glaucoma is provided. The implant includes a longitudinal implant axis and comprises a first portion at a first end of said longitudinal implant axis. The first portion is sized and configured to reside in Schlemm's canal, such that said first portion has a maximum dimension along a longitudinal axis of Schlemm's canal that is not substantially greater than a dimension of the first portion that runs perpendicular to both said longitudinal axis of Schlemm's canal and to said longitudinal implant axis. A second portion at a second end of said longitudinal implant axis is configured to provide fluid communication between the anterior chamber and said first portion.

In accordance with yet another embodiment of at least one of the inventions disclosed herein, an implant for treating glaucoma comprises an outflow portion, sized and shaped to be received within Schlemm's canal. An inflow portion is in fluid communication with said outflow portion, the inflow portion configured to be disposed in the anterior chamber of the eye. A central portion extending between the inflow and outflow portions. The outflow portion having a diameter that is no more than three times the diameter of the central portion.

In accordance with yet another embodiment of at least one of the inventions disclosed herein, an instrument for delivering implants for treating an ophthalmic condition is provided. The instrument comprises an elongate body sized to be introduced into an eye through an incision in the eye. A plurality of implants is positioned in the elongate body. The elongate body further comprises an actuator that serially dispenses the implants from the elongate body for implanting in eye tissue.

In accordance with another embodiment of at least one of the inventions disclosed herein, a method of implanting a plurality of implants for treating glaucoma is provided. The method includes inserting an instrument into an eye through an incision, utilizing the instrument to deliver a first implant through a wall of Schlemm's canal at a first location, and utilizing the instrument to deliver a second implant through a wall of Schlemm's canal at a second location, without removing the instrument from the eye between the deliveries of said implants.

In accordance with yet another embodiment of at least one of the inventions disclosed herein, a method of implanting a plurality of implants for treating glaucoma is provided. The method includes inserting an instrument into an eye through an incision, utilizing the instrument to deliver a first implant through a wall of Schlemm's canal at a first location, and utilizing the instrument to deliver a second implant through a wall of Schlemm's canal at a second location, wherein the locations are determined from morphological data on collector channel locations.

In accordance with yet another embodiment of at least one of the inventions disclosed herein, a method of implanting a plurality of implants for treating glaucoma is provided. The method comprises inserting an instrument into an eye through an incision, utilizing the instrument to deliver a first implant through a wall of Schlemm's canal at a first location, and utilizing said instrument to deliver a second implant through a wall of Schlemm's canal at a second location. The locations are determined by imaging collector channel locations.

In accordance with a further embodiment of at least one of the inventions disclosed herein, a method of implanting a plurality of implants for treating glaucoma is provided. The method comprises inserting an instrument into an eye through an incision, utilizing the instrument to deliver a first implant through a wall of Schlemm's canal at a first location, and utilizing said instrument to deliver a second implant through a wall of Schlemm's canal at a second location. The locations are angularly spaced along Schlemm's canal by at least 20 degrees.

In accordance with yet another embodiment of at least one of the inventions disclosed herein, a method of implanting a plurality of implants for treating glaucoma is provided. The method comprises inserting an instrument into an eye through an incision, utilizing the instrument to deliver a first implant through a wall of Schlemm's canal at a first location, utilizing the instrument to deliver a second implant through a wall of Schlemm's canal at a second location. The first and second locations are substantially at collector channels.

In accordance with another embodiment of at least one of the inventions disclosed herein, a method of implanting a plurality of implants for treating glaucoma is provided. The method comprises inserting an instrument into an eye through an incision, utilizing the instrument to deliver a first implant through a wall of Schlemm's canal at a first location, and utilizing said instrument to deliver a second implant through a wall of Schlemm's canal at a second location. The implants have different flow characteristics.

In accordance with yet another embodiment of at least one of the inventions disclosed herein, a method of implanting a plurality of implants for treating glaucoma is provided. The method comprises inserting an instrument into an eye through an incision, utilizing the instrument to deliver a first implant into the posterior segment of the eye, and utilizing the instrument to deliver a second implant into the posterior segment of the eye at a second location. The instrument is not removed from the eye between said deliveries of the implants.

In accordance with a further embodiment of at least one of the inventions disclosed herein, a method of implanting a plurality of implants for treating glaucoma is provided. The method comprises serially dispensing a plurality of preloaded implants from an instrument into eye tissue at a respective plurality of locations within the eye.

For purposes of summarizing, certain aspects, advantages and novel features of the inventions disclosed herein have been described herein above. Of course, it is to be understood that not necessarily all such advantages may be achieved in accordance with any particular embodiment. Thus, the inventions may be embodied or carried out in a manner that achieves or optimizes one advantage or group of advantages as taught or suggested herein without necessarily achieving other advantages as may be taught or suggested herein.

Some embodiments include an implant for treating glaucoma, comprising a body comprising material that includes a drug, the body having an inlet portion and an outlet portion, the inlet portion configured to transport fluid from the anterior chamber of an eye to the outlet portion when the outlet portion is disposed in Schlemm's canal of the eye, the outlet portion having an outflow opening.

In some embodiments, the body is coated with the drug. In some embodiments, the drug comprises heparin.

Some embodiments include an implant for treating glaucoma, comprising a body having a bioactive agent in or on the body, the body having an inlet portion and an outlet portion, the inlet portion configured to transmit fluid from the anterior chamber to the outlet portion when the outlet portion is disposed in Schlemm's canal, the outlet portion having an outflow opening.

In some embodiments, the bioactive agent comprises TGF-beta, a gene, an anti-inflammatory drug, and/or an intraocular pressure-lowering drug.

In some embodiments, the bioactive agent comprises a growth factor and/or an antiproliferative agent.

In some embodiments, the bioactive agent is loaded onto a surface of the outlet section.

Some embodiments further comprise a biodegradable material in or on the implant. In some embodiments, the biodegradable material is selected from the group consisting of poly(lactic acid), polyethylene-vinyl acetate, poly(lactic-co-glycolic acid), poly(D,L-lactide), poly(D,L-lactide-co-trimethylene carbonate), collagen, heparinized collagen, poly (caprolactone), poly(glycolic acid), and a copolymer.

In some embodiments, the outlet end further comprises a plurality of pillars at the outlet end. In some embodiments, the bioactive agent is in or on at least one of the pillars.

In some embodiments, the implant is at least partially coated with at least one polymer film that contains the bioactive agent, the polymer film permitting a delivery of a quantity of the bioactive agent to ocular tissues over time.

Some embodiments include an ocular implant comprising a body having a bioactive agent in or on the body, the body further comprising an inlet section configured to be positioned in the anterior chamber of an eye; an outlet section configured to be positioned at least partially in Schlemm's canal of the eye, the outlet section being in fluid communication with the inlet section; a lumen extending between the inlet section and the outlet section; and a flow-restricting member within the lumen, the flow-restricting member being configured to prevent at least one component of blood from passing through the flow-restricting member.

In some embodiments, the bioactive agent comprises an Imidazole antiproliferative agent, a quinoxaline, a phosphonylmethoxyalkyl nucleotide analog, a potassium channel blocker, and/or a synthetic oligonucleotide. In some embodiments, the bioactive agent comprises 5-[1-hydroxy-2-[2-(2-methoxyphenoxyl)ethylamino]ethyl]-2-methylbenzene-sulfonamide.

In some embodiments, the bioactive agent comprises a guanylate cyclase inhibitor, such as methylene blue, butylated hydroxyanisole, and/or N-methylhydroxylamine. In some embodiments, the bioactive agent comprises 2-(4-methylaminobutoxy) diphenylmethane. In some embodiments, the bioactive agent comprises a combination of apraclonidine and timolol.

In some embodiments, the bioactive agent comprises a cloprostenol analog or a fluprostenol analog. In some embodiments, the bioactive agent comprises a crosslinked carboxy-containing polymer, a sugar, and water. In some embodiments, the bioactive agent comprises a non-corneotoxic serine-threonine kinase inhibitor. In some embodiments, the bioactive agent comprises a nonsteroidal glucocorticoid antagonist. In some embodiments, the bioactive agent comprises a prostaglandin analog or a derivative thereof.

These and other embodiments of the inventions will become apparent to those skilled in the art from the following detailed description of exemplary embodiments having reference to the attached figures, the inventions not being limited to any particular preferred embodiment(s) disclosed.

BRIEF DESCRIPTION OF THE DRAWINGS

Certain preferred embodiments and modifications thereof will become apparent to those skilled in the art from the detailed description herein having reference to the figures that follow, of which:

FIG. **1** is a coronal cross-sectional view of an eye.

FIG. **2** is an enlarged cross-sectional view of an anterior chamber angle of the eye of FIG. **1** with a trabecular stent.

FIG. **3** is a schematic and partial sectional view of an eye illustrating an implanted glaucoma stent in accordance with one embodiment of at least one of the inventions disclosed herein.

FIG. **4** is a side elevational view of the stent of FIG. **3**.

FIG. **5** is a top plan view of the stent of FIG. **3**.

FIG. **6** is a bottom plan view of the stent of FIG. **3**.

FIG. **7** is a front elevational view of the stent of FIG. **3** (along line **7-7** of FIG. **4**).

FIG. **8** is a rear elevational view of the stent of FIG. **3** (along line **8-8** of FIG. **4**).

FIG. **9** is an enlarged top plan view of a forward end of the stent of FIG. **3**.

FIG. **10** is a top plan view of a modification of an inlet end of the stent of FIG. **3**.

FIG. **11** is a top plan view of another modification of the inlet end of the stent of FIG. **3**.

FIG. **12** is a top plan view of yet another modification of the inlet end of the stent of FIG. **3**.

FIG. **13** is a top plan view of still another modification of the inlet end of the stent of FIG. **3**.

FIG. **14** is schematic and partial sectional view of an eye illustrating a modification of the implanted glaucoma stent of FIG. **3**.

FIG. **15** is a schematic and partial sectional view of an eye illustrating a further modification of the implanted glaucoma stent of FIG. **3**.

FIG. **16** is a side elevational view of yet another modification of the glaucoma stent of FIG. **3**.

FIG. **17** is a top plan view of the stent of FIG. **16**.

FIG. **18** is a bottom plan view of the stent of FIG. **16**.

FIG. **19** is a front elevational view along line **19-19** of FIG. **16**.

FIG. **20** is a rear elevational view along line **20-20** of FIG. **16**.

FIG. **21** is a side elevation view of still another modification of the glaucoma stent of FIG. **3**.

FIG. **22** is a top plan view of the stent of FIG. **21**.

FIG. **23** is a bottom plan view of the stent of FIG. **21**.

FIG. **24** is a front elevational view along line **24-24** of FIG. **21**.

FIG. **25** is a rear elevational view along line **25-25** of FIG. **21**.

FIG. **26** is a front elevational view of a modification of the glaucoma stent illustrated in FIG. **3**.

FIG. **27** is a right side elevational view of the stents illustrated in FIG. **26** as viewed along the line **27-27**.

FIG. **28** is a right side elevational view of the glaucoma stent illustrated in FIG. **26**, as viewed along the line **28-28**.

FIG. **29** is a schematic and partial sectional view of an eye illustrating a temporal implantation of a glaucoma stent, using a delivery apparatus having features and advantages in accordance with at least one of the inventions disclosed herein.

FIG. **30** is an oblique elevational view of an articulating arm stent delivery/retrieval apparatus having features and advantages in accordance with an embodiment of at least one of the inventions disclosed herein.

FIG. **31** is a schematic and partial sectional view of a portion of an eye and illustrating an implantation of a glaucoma stent using a delivery apparatus extending through the anterior chamber of the eye.

FIG. **32** is a schematic and partial sectional view of a Schlemm's canal and trabecular meshwork of an eye with another glaucoma stent extending from the anterior chamber of the eye, through the trabecular meshwork, and into a rear wall of the Schlemm's canal.

FIG. **33** is an enlarged cross-sectional view of a distal portion of the stent illustrated in FIG. **32**.

FIG. **34** is a schematic and partial sectional view of the eye of FIG. **32** and a side elevational view of a modification of the stent illustrated in FIG. **32**.

FIG. **35** is a schematic and partial sectional view of the eye illustrated in FIG. **32**, and a side elevational view of a photo-modification of the stent illustrated in FIG. **32**.

FIG. **36** is a schematic and partial sectional view of the eye illustrated in FIG. **32**, and a side elevational view of another modification of the stent of FIG. **32**.

FIG. **37** is a schematic and partial sectional view of the eye illustrated in FIG. **32**, and a side elevational view of a further modification of the implant illustrated in FIG. **32**.

FIG. **38** is a schematic and partial sectional view of the eye illustrated in FIG. **32** and a side elevational view of another modification of the stent illustrated in FIG. **32**.

FIG. **39** is a schematic and partial sectional view of the eye illustrated in FIG. **32**, and a side elevational view of the further modification of the implant illustrated in FIG. **32**.

FIG. **40** is a schematic and partial sectional view of the eye illustrated in FIG. **32**, and a side elevational view of yet another modification of the stent illustrated in FIG. **32**.

FIG. **41** is a schematic and partial sectional view of an eye and the side elevational view of yet another modification of the stent illustrated in FIG. **32**.

FIG. **42** is a schematic and partial sectional view of the eye illustrated in FIG. **32**, and a side elevational view of yet another modification of the implant illustrated in FIG. **32**.

FIG. **43** is an enlarged schematic and partial cross-sectional view of an anterior chamber angle of an eye having a valve stent implanted therein.

FIG. **44** is an enlarged cross-sectional view of an anterior chamber angle of an eye including an osmotic membrane device implanted therein.

FIG. **45** is an enlarged cross-sectional view of an anterior chamber angle of an eye illustrating an implantation of a glaucoma stent using an ab externo procedure.

FIG. **46** is a schematic and partial sectional view of the eye illustrated in FIG. **32** and a side elevational view of another modification of the implant illustrated in FIG. **32**.

FIG. **47** is an enlarged schematic and partial sectional view of the eye illustrated in FIG. **32** and including a drug release device implanted therein.

FIG. **48** is a flow diagram illustrating a method for treating glaucoma.

FIG. **49**A is an enlarged schematic illustration showing an anterior chamber, trabecular meshwork and a Schlemm's canal of an eye and an oblique elevational view of yet another modification of the stent illustrated in FIG. **32**.

FIG. **49**B is an oblique elevational view of a modification of the stent illustrated in FIG. **49**A.

FIG. **49**C is a side elevational view of another modification of the stent illustrated in FIG. **49**A.

FIG. **50**A is a cross-sectional view of the eye portion showing anatomically the trabecular meshwork, Schlemm's canal and one collector duct.

FIG. **50**B is a cross-sectional view of FIG. **50**A with a portion of a stent mechanically inserted into one of the collector ducts.

FIG. **51**A is a side elevational view of a stent delivery applicator with a steerable distal section for multiple stent deployment.

FIG. **51**B is a schematic and partial sectional view of the distal section of the stent delivery applicator of FIG. **51**A.

FIG. **51**C is a cross-sectional view, section **1-1** of FIG. **51**B.

FIG. **51**D is an oblique side elevational view of the steerable section of the delivery applicator illustrated in FIG. **51**A and including an optional ultrasonically enabled distal end.

FIG. **52**A is a partial sectional and side elevational view of a distal section of a modification of the stent delivery applicator illustrated in FIG. **51**A.

FIG. **52**B is a partial sectional and side elevational view of a distal section of the stent delivery applicator illustrated in FIG. **51**A having been inserted through a trabecular meshwork with the stent disposed within the distal section.

FIG. **52**C is a partial sectional and side elevational view of a distal section of the stent delivery applicator illustrated in FIG. **51**A having been inserted through a trabecular meshwork and after the sheath of the distal portion has been withdrawn.

FIG. **52**D is a partial sectional and side elevational view of a distal section of the stent delivery applicator illustrated in FIG. **51**A having been inserted through a trabecular meshwork, and after the sheath and a cutting member have been withdrawn.

FIG. **53** is an oblique side elevational and partial sectional view of a further modification of the stent illustrated in FIG. **32**.

FIG. **54**A is a sectional view of yet another modification of the stent delivery applicator illustrated in FIG. **51**A.

FIG. **54**B is an enlarged sectional view of a distal end of the applicator illustrated in FIG. **54**A and including two implants disposed over a trocar of the device, this portion being identified by the circle **2-2** in FIG. **54**A.

FIG. **54**C is a sectional view of the applicator device taken along section line **3-3** of FIG. **54**A.

FIG. **55** shows an embodiment of a seton implant constructed according to the principles of the invention.

FIG. **56** is a top cross-sectional view of section **1-1** of FIG. **55**.

FIG. **57** is another embodiment of a seton implant constructed in accordance with the principles of the invention.

FIG. **58** is an oblique elevation view of one embodiment of a trabecular stenting device.

FIG. **59** is an oblique elevation view of another embodiment of a trabecular stenting device.

FIG. **60** is an oblique elevation view of placement of one end of a trabecular stenting device through a trabecular meshwork.

FIG. **61** is an oblique elevation view of placement of one end of a trabecular stenting device through a trabecular meshwork, wherein the trabecular stenting device is passed over a guidewire.

FIG. **62** is an oblique elevation view of a preferred implantation of a trabecular stenting device through a trabecular meshwork.

FIG. **63** is a close-up, cut-away view of an inlet section of the trabecular stenting device of FIGS. **58** and **59**, illustrating a flow-restricting member retained within a lumen of the trabecular stenting device.

FIG. **64** is one embodiment of an axisymmetric trabecular stenting device for incorporating bioactive agents.

FIG. **65** is one embodiment of a fistula without a lumen for transporting aqueous and carrying bioactive agents of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred embodiments described herein relate particularly to surgical and therapeutic treatment of glaucoma through reduction of intraocular pressure and/or stimulation

of the trabecular meshwork tissue. While the description sets forth various embodiment-specific details, it will be appreciated that the description is illustrative only and should not be construed in any way as limiting the invention. Furthermore, various applications of the inventions disclosed herein, and modifications thereto, which may occur to those who are skilled in the art, are also encompassed by the general concepts described herein.

FIG. **1** is a cross-sectional view of an eye **10**. FIG. **2** is an enlarged sectional view of the eye showing the relative anatomical locations of a trabecular meshwork **21**, an anterior chamber **20**, and a Schlemm's canal **22**. A sclera **11** is a thick collagenous tissue that covers the entire eye **10** except a portion that is covered by a cornea **12**.

With reference to FIGS. **1** and **2**, the cornea **12** is a thin transparent tissue that focuses and transmits light into the eye and through a pupil **14**, which is a circular hole in the center of an iris **13** (colored portion of the eye). The cornea **12** merges into the sclera **11** at a juncture referred to as a limbus **15**. A ciliary body **16** extends along the interior of the sclera **11** and is coextensive with a choroid **17**. The choroid **17** is a vascular layer of the eye **10**, located between the sclera **11** and a retina **18**. An optic nerve **19** transmits visual information to the brain and is the anatomic structure that is progressively destroyed by glaucoma.

With continued reference to FIGS. **1** and **2**, the anterior chamber **20** of the eye **10**, which is bound anteriorly by the cornea **12** and posteriorly by the iris **13** and a lens **26**, is filled with aqueous humor (hereinafter referred to as "aqueous"). Aqueous is produced primarily by the ciliary body **16**, then moves anteriorly through the pupil **14** and reaches an anterior chamber angle **25**, formed between the iris **13** and the cornea **12**.

As best illustrated by the drawing of FIG. **2**, in a normal eye, aqueous is removed from the anterior chamber **20** through the trabecular meshwork **21**. Aqueous passes through the trabecular meshwork **21** into Schlemm's canal **22** and thereafter through a plurality of collector ducts and aqueous veins **23**, which merge with blood-carrying veins, and into systemic venous circulation. Intraocular pressure is maintained by an intricate balance between secretion and outflow of aqueous in the manner described above. Glaucoma is, in most cases, characterized by an excessive buildup of aqueous in the anterior chamber **20**, which leads to an increase in intraocular pressure. Fluids are relatively incompressible, and thus intraocular pressure is distributed relatively uniformly throughout the eye **10**.

As shown in FIG. **2**, the trabecular meshwork **21** is adjacent a small portion of the sclera **11**. Exterior to the sclera **11** is a conjunctiva **24**. Traditional procedures that create a hole or opening for implanting a device through the tissues of the conjunctiva **24** and sclera **11** involve extensive surgery, as compared to surgery for implanting a device, as described herein, which ultimately resides entirely within the confines of the sclera **11** and cornea **12**. A trabecular stent **229** can be placed bypassing the trabecular meshwork **21** with a proximal terminal **227** exposed to anterior chamber **20** and a distal terminal **228** exposed to Schlemm's canal **22**.

FIG. **3** schematically illustrates the use of one embodiment of a trabecular stenting device **30** for establishing an outflow pathway, passing through the trabecular meshwork **21**, described in greater detail below. FIGS. **4-9** are different views of the stent **30**. Advantageously, and as discussed in further detail later herein, the self-trephining-stent allows a one-step procedure to make an incision in the trabecular mesh **21** and place the stent or implant **30** at the desired or predetermined position within the eye **10**. Desirably, this facilitates and simplifies the overall surgical procedure.

In the illustrated embodiment of FIGS. **3-9**, the shunt or stent **30** generally comprises an inlet portion or "snorkel" **32** and a main body portion or blade **34**. The snorkel **32** and blade **34** are mechanically connected to or in mechanical communication with one another. A generally longitudinal axis **36** extends along the stent **30** and/or the body portion **34**.

In the illustrated embodiment of FIGS. **3-9**, the stent **30** comprises an integral unit. In modified embodiments, the stent **30** may comprise an assembly of individual pieces or components. For example, the stent **30** may comprise an assembly of the snorkel **32** and blade **34**.

In the illustrated embodiment of FIGS. **3-9**, the snorkel **32** is in the form of a generally elongate tubular member and generally comprises an upper seat, head or cap portion **38**, a shank portion **40** and a lumen or passage **42** extending therethrough. The seat **38** is mechanically connected to or in mechanical communication with the shank **40**, which is also mechanically connected to, or in mechanical communication with the blade **34**. The longitudinal axis **43** extends along the snorkel **32** and/or the lumen **42**.

In the illustrated embodiment of FIGS. **3-9**, the seat **38** is generally circular in shape and has an upper surface **44** and a lower surface **46**, which, as shown in FIG. **3**, abuts or rests against the trabecular meshwork **21** to stabilize the glaucoma stent **30** within the eye **10**. In modified embodiments, the seat **38** may efficaciously be shaped in other suitable manners, as required or desired, giving due consideration to the goals of stabilizing the glaucoma stent **30** within the eye **10** and/or of achieving one or more of the benefits and advantages as taught or suggested herein. For example, the seat **38** may be shaped in other polygonal or non-polygonal shapes and/or comprise one or more ridges which extend radially outwards, among other suitable retention devices.

In the illustrated embodiment of FIGS. **3-9**, and as best seen in the top view of FIG. **5**, the seat top surface **44** comprises fiducial marks or indicia **48**. These marks or indicia **48** facilitate and ensure proper orientation and alignment of the stent **30** when implanted in the eye **10**. The marks or indicia **48** may comprise visual differentiation means such as color contrast or be in the form of ribs, grooves, or the like. Alternatively, or in addition, the marks **48** may provide tactile sensory feedback to the surgeon by incorporating a radiopaque detectable or ultrasound imaginable substrate at about the mark **48**. Also, the seat **38** and/or the seat top surface **44** may be configured in predetermined shapes aligned with the blade **34** and/or longitudinal axis **36** to provide for proper orientation of the stent device **30** within the eye **10**. For example, the seat top surface **44** may be oval or ellipsoidal (FIG. **10**), rectangular (FIG. **11**), hexagonal (FIG. **12**), among other suitable shapes (e.g. FIG. **13**).

In the illustrated embodiment of FIGS. **3-9**, and as indicated above, the seat bottom surface **46** abuts or rests against the trabecular meshwork **21** to stabilize and retain the glaucoma stent **30** within the eye **10**. For stabilization purposes, the seat bottom surface **46** may comprise a studded surface, a ribbed surface, a surface with pillars, a textured surface, or the like.

In the illustrated embodiment of FIGS. **3-9**, the snorkel shank **40** is generally cylindrical in shape. With the stent **30** implanted, as shown in FIG. **3**, the shank **40** is generally positioned in an incision or cavity **50** formed in the trabecular meshwork **21** by the self-trephining stent **30**. Advantageously, and as discussed further below, this single step of forming the cavity **50** by the stent **30** itself and placing the stent **30** in the desired position facilitates and expedites the

overall surgical procedure. In modified embodiments, the snorkel shank **40** may efficaciously be shaped in other suitable manners, as required or desired. For example, the shank **40** may be in the shape of other polygonal or non-polygonal shapes, such as, oval, ellipsoidal, and the like.

In the illustrated embodiment of FIGS. **3-9**, and as best seen in FIG. **3**, the shank **40** has an outer surface **52** in contact with the trabecular meshwork **21** surrounding the cavity **50**. For stabilization purposes, the shank outer surface **52** may comprise a studded surface, a ribbed surface, a surface with pillars, a textured surface, or the like.

In the illustrated embodiment of FIGS. **3-9**, the snorkel lumen **42** has an inlet port, opening or orifice **54** at the seat top surface **44** and an outlet port, opening or orifice **56** at the junction of the shank **40** and blade **34**. The lumen **42** is generally cylindrical in shape, that is, it has a generally circular cross-section, and its ports **54**, **56** are generally circular in shape. In modified embodiments, the lumen **42** and ports **54**, **56** may be efficaciously shaped in other manners, as required or desired, giving due consideration to the goals of providing sufficient aqueous outflow and/or of achieving one or more of the benefits and advantages as taught or suggested herein. For example, the lumen **42** and/or one or both ports **54**, **56** may be shaped in the form of ovals, ellipsoids, and the like, or the lumen **42** may have a tapered or stepped configuration.

Referring in particular to FIG. **3**, aqueous from the anterior chamber **20** flows into the lumen **42** through the inlet port **54** (as generally indicated by arrow **58**) and out of the outlet port **56** and into Schlemm's canal **22** (as generally indicated by arrows **60**) to lower and/or balance the intraocular pressure (IOP). In another embodiment, as discussed in further detail below, one or more of the outlet ports may be configured to face in the general direction of the stent longitudinal axis **36**. In modified embodiments, the snorkel **32** may comprise more than one lumen, as needed or desired, to facilitate multiple aqueous outflow transportation into Schlemm's canal **22**.

In the illustrated embodiment of FIGS. **3-9**, the blade longitudinal axis **36** and the snorkel longitudinal axis **43** are generally perpendicular to one another. Stated differently, the projections of the axes **36**, **43** on a common plane which is not perpendicular to either of the axes **36**, **43** intersect at 90°. The blade longitudinal axis **36** and the snorkel longitudinal axis **43** may intersect one another or may be offset from one another.

In the illustrated embodiment of FIGS. **3-9**, the main body portion or blade **34** is a generally curved elongated sheet- or plate-like structure with an upper curved surface **62** and a lower curved surface **64**, which defines a trough or open face channel **66**. The perimeter of the blade **34** is generally defined by a curved proximal edge **68** proximate to the snorkel **32**, a curved distal edge **70** spaced from the proximal edge **68** by a pair of generally straight lateral edges **72**, **74**. The first lateral edge **72** extends beyond the second lateral edge **74** and intersects with the distal edge **70** at a distal-most point **76** of the blade **34**. Preferably, the blade **34** defines a blade cutting tip **78**.

In the illustrated embodiment of FIGS. **3-9**, and as shown in the enlarged view of FIG. **9**, the cutting tip **78** comprises a first cutting edge **80** on the distal edge **70** and a second cutting edge **82** on the lateral edge **72**. The cutting edges **80**, **82** preferably extend from the distal-most point **76** of the blade **34** and comprise at least a respective portion of the distal edge **70** and lateral edge **72**. The respective cutting edges **80**, **82** are formed at the sharp edges of respective beveled or tapered surfaces **84**, **86**. In one embodiment, the remainder of the distal edge **70** and lateral edge **72** are dull or rounded. In one embodiment, the tip **78** proximate to the distal-most end **76** is curved slightly inwards, as indicated generally by the arrow **88** in FIG. **5** and arrow **88** (pointed perpendicular and into the plane of the paper) in FIG. **9**, relative to the adjacent curvature of the blade **34**.

In modified embodiments, suitable cutting edges may be provided on selected portions of one or more selected blade edges **68**, **70**, **72**, **74** with efficacy, as needed or desired, giving due consideration to the goals of providing suitable cutting means on the stent **30** for effectively cutting through the trabecular meshwork **21** (FIG. **3**) and/or of achieving one or more of the benefits and advantages as taught or suggested herein.

Referring in particular to FIG. **9**, in one embodiment, the ratio between the lengths of the cutting edges **80**, **82** is about 2:1. In another embodiment, the ratio between the lengths of the cutting edges **80**, **82** is about 1:1. In yet another embodiment, the ratio between the lengths of the cutting edges **80**, **82** is about 1:2. In modified embodiments, the lengths of the cutting edges **80**, **82** may be efficaciously selected in other manners, as required or desired, giving due consideration to the goals of providing suitable cutting means on the stent **30** for effectively cutting through the trabecular meshwork **21** (FIG. **3**) and/or of achieving one or more of the benefits and advantages as taught or suggested herein.

Still referring in particular to FIG. **9**, in one embodiment, the ratio between the lengths of the cutting edges **80**, **82** is in the range from about 2:1 to about 1:2. In another embodiment, the ratio between the lengths of the cutting edges **80**, **82** is in the range from about 5:1 to about 1:5. In yet another embodiment, the ratio between the lengths of the cutting edges **80**, **82** is in the range from about 10:1 to about 1:10. In modified embodiments, the lengths of the cutting edges **80**, **82** may be efficaciously selected in other manners, as required or desired, giving due consideration to the goals of providing suitable cutting means on the stent **30** for effectively cutting through the trabecular meshwork **21** (FIG. **3**) and/or of achieving one or more of the benefits and advantages as taught or suggested herein.

As shown in the top view of FIG. **9**, the cutting edge **80** (and/or the distal end **70**) and the cutting edge **82** (and/or the lateral edge **72**) intersect at an angle θ. Stated differently, θ is the angle between the projections of the cutting edge **80** (and/or the distal end **70**) and the cutting edge **82** (and/or the lateral edge **72**) on a common plane that is not perpendicular to either of these edges.

Referring to in particular to FIG. **9**, in one embodiment, the angle θ is about 50°. In another embodiment, the angle θ is in the range from about 40° to about 60°. In yet another embodiment, the angle θ is in the range from about 30° to about 70°. In modified embodiments, the angle θ may be efficaciously selected in other manners, as required or desired, giving due consideration to the goals of providing suitable cutting means on the stent **30** for effectively cutting through the trabecular meshwork **21** (FIG. **3**) and/or of achieving one or more of the benefits and advantages as taught or suggested herein.

The stent **30** of the embodiments disclosed herein can be dimensioned in a wide variety of manners. Referring in particular to FIG. **3**, the depth of Schlemm's canal **22** is typically about less than 400 microns (μm). Accordingly, the stunt blade **34** is dimensioned so that the height of the blade **34** (referred to as H_{41} in FIG. **4**) is typically less than about 400 μm. The snorkel shank **40** is dimensioned so that it has a length (referred to as L_{41} in FIG. **4**) typically in the range from about 150 μm to about 400 μm, which is roughly the typical range of the thickness of the trabecular meshwork **21**.

Of course, as the skilled artisan will appreciate, that with the stent **30** implanted, the blade **34** may rest at any suitable position within Schlemm's canal **22**. For example, the blade

34 may be adjacent to a front wall 90 of Schlemm's canal 22 (as shown in FIG. 3), or adjacent to a back wall 92 of Schlemm's canal 22, or at some intermediate location therebetween, as needed or desired. Also, the snorkel shank 40 may extend into Schlemm's canal 22. The length of the snorkel shank 40 and/or the dimensions of the blade 34 may be efficaciously adjusted to achieve the desired implant positioning.

The trabecular stenting device 30 (FIGS. 3-9) of the exemplary embodiment may be manufactured or fabricated by a wide variety of techniques. These include, without limitation, molding, thermo-forming, or other micro-machining techniques, among other suitable techniques.

The trabecular stenting device 30 preferably comprises a biocompatible material such that inflammation arising due to irritation between the outer surface of the device 30 and the surrounding tissue is minimized. Biocompatible materials which may be used for the device 30 preferably include, but are not limited to, titanium, titanium alloys, medical grade silicone, e.g., Silastic™, available from Dow Corning Corporation of Midland, Mich.; and polyurethane, e.g., Pellethane™, also available from Dow Corning Corporation.

In other embodiments, the stent device 30 may comprise other types of biocompatible material, such as, by way of example, polyvinyl alcohol, polyvinylpyrrolidone, collagen, heparinized collagen, polytetrafluoroethylene, expanded polytetrafluoroethylene, fluorinated polymer, fluorinated elastomer, flexible fused silica, polyolefin, polyester, polysilicon, and/or a mixture of the aforementioned biocompatible materials, and the like. In still other embodiments, composite biocompatible material may be used, wherein a surface material may be used in addition to one or more of the aforementioned materials. For example, such a surface material may include polytetrafluoroethylene (PTFE) (such as Teflon™), polyimide, hydrogel, heparin, therapeutic drugs (such as beta-adrenergic antagonists and other anti-glaucoma drugs, or antibiotics), and the like.

In an exemplary embodiment of the trabecular meshwork surgery, the patient is placed in the supine position, prepped, draped and anesthetized as necessary. A small (less than about 1 mm) incision, which may be self sealing, can then be made through the cornea 12. The corneal incision can be made in a number of ways, for example, by using a micro-knife, among other tools.

An applicator or delivery apparatus is used to advance the glaucoma stent 30 through the corneal incision and to the trabecular meshwork 21. Some embodiments of such a delivery apparatus are disclosed in copending U.S. application Ser. No. 10/101,548, filed Mar. 18, 2002, entitled APPLICATOR AND METHODS FOR PLACING A TRABECULAR SHUNT FOR GLAUCOMA TREATMENT, and U.S. Provisional Application No. 60/276,609, filed Mar. 16, 2001, entitled APPLICATOR AND METHODS FOR PLACING A TRABECULAR SHUNT FOR GLAUCOMA TREATMENT, the entire contents of each one of which are hereby incorporated by reference herein. Some embodiments of a delivery apparatus are also described in further detail below. Gonioscopic, microscopic, or endoscopic guidance can be used during the trabecular meshwork surgery.

With the device 30 held by the delivery apparatus, the blade 34 of the device 30 is used to cut and/or displace the material of the trabecular meshwork 21. The snorkel shank 40 can also facilitate in removal of this material during implantation. The delivery apparatus is withdrawn once the device 30 has been implanted in the eye 10. As shown in FIG. 3, the snorkel seat 38 can rest on a top surface 94 of the trabecular meshwork 21 with the snorkel shank 40 extending through the cavity 50 (created by the device 30) in the trabecular meshwork 21, and with the blade 34 extending inside Schlemm's canal 22.

Advantageously, the embodiments of the self-trephining stent device 30 allow for a "one-step" procedure to make an incision in the trabecular meshwork and to implant the stent in the proper orientation and alignment within the eye to allow outflow of aqueous from the anterior chamber through the stent and into Schlemm's canal to lower and/or balance the intraocular pressure (IOP). Desirably, this provides for a faster, safer, and less expensive surgical procedure.

Many complications can arise in trabecular meshwork surgeries, wherein a knife is first used to create an incision in the trabecular meshwork, followed by removal of the knife and subsequent installation of the stent. For instance, the knife may cause some bleeding which clouds up the surgical site. This may require more effort and time to clean the surgical site prior to placement of the stent. Moreover, this may cause the intraocular pressure (IOP) to rise or to fall undesirably. Thus, undesirably, such a multiple step procedure may demand crisis management that slows down the surgery, makes it less safe, and more expensive.

FIG. 14 is a simplified partial view of an eye 10 illustrating the implantation of a self-trephining glaucoma stent device 30*a* having features and advantages in accordance with one embodiment. The stent 30*a* is generally similar to the stent 30 of FIGS. 3-9 except that its snorkel 32*a* comprises a longer shank 40*a*, which extends into Schlemm's canal 22 and a lumen 42*a*, which bifurcates into two output channels 45*a*.

In the illustrated embodiment of FIG. 14, the shank 40*a* terminates at the blade 34. Aqueous flows from the anterior chamber 20 into the lumen 42*a* through an inlet port 54*a* (as generally indicated by arrow 58*a*). Aqueous then flows through the output channels 45*a* and out of respective outlet ports 56*a* and into Schlemm's canal 22 (as generally indicated by arrows 60*a*). The outlet channels 45*a* extend radially outwards in generally opposed directions and the outlet ports 56*a* are configured to face in the general direction of the stent longitudinal axis 36 so that they open into Schlemm's canal 22 and are in proper orientation to allow aqueous outflow into Schlemm's canal 22 for lowering and/or balancing the intraocular pressure (IOP). As indicated above, fiducial marks or indicia and/or predetermined shapes of the snorkel seat 38 allow for proper orientation of the blade 34 and also the output channels 45*a* and respective ports 56*a* within Schlemm's canal.

In the illustrated embodiment of FIG. 14, two outflow channels 45*a* are provided. In another embodiment, only one outflow channel 45*a* is provided. In yet another embodiment, more than two outflow channels 45*a* are provided. In modified embodiments, the lumen 42*a* may extend all the way through to the blade 34 and provide an outlet port as discussed above with reference to the embodiment of FIGS. 3-9.

FIG. 15 is a simplified partial view of an eye 10 illustrating the implantation of a self-trephining glaucoma stent device 30*b* having features and advantages in accordance with one embodiment. The stent 30*b* is generally similar to the stent 30 of FIGS. 3-9 except that its snorkel 32*b* comprises a longer shank 40*b*, which extends into Schlemm's canal 22 and a lumen 42*b*, which bifurcates into two output channels 45*b*.

In the illustrated embodiment of FIG. 15, the shank 40*b* extends through the blade 34. Aqueous flows from the anterior chamber 20 into the lumen 42*b* through an inlet port 54*b* (as generally indicated by arrow 58*b*). Aqueous then flows through the output channels 45*b* and out of respective outlet ports 56*b* and into Schlemm's canal 22 (as generally indicated by arrows 60*b*). The outlet channels 45*b* extend radially outwards in generally opposed directions and the outlet ports

56*b* are configured to face in the general direction of the stent longitudinal axis **36** so that they open into Schlemm's canal **22** and are in proper orientation to allow aqueous outflow into Schlemm's canal **22** for lowering and/or balancing the intraocular pressure (IOP). As indicated above, fiducial marks or indicia and/or predetermined shapes of the snorkel seat **38** allow for proper orientation of the blade **34** and also the output channels **45***b* and respective ports **56***b* within Schlemm's canal.

In the illustrated embodiment of FIG. **15**, two outflow channels **45***b* are provided. In another embodiment, only one outflow channel **45***b* is provided. In yet another embodiment, more than two outflow channels **45***b* are provided. In modified embodiments, the lumen **42***b* may extend all the way through to the blade **34** and provide an outlet port as discussed above with reference to the embodiment of FIGS. **3-9**.

FIGS. **16-20** show different views of a self-trephining glaucoma stent device **30***c* having features and advantages in accordance with one embodiment. The stent **30***c* is generally similar to the stent **30** of FIGS. **3-9** except that it has a modified blade configuration. The stent **30***c* comprises a blade **34***c* which is a generally curved elongated sheet- or plate-like structure with an upper curved surface **62***c* and a lower curved surface **64***c* which defines a trough or open face channel **66***c*. The perimeter of the blade **34***c* is generally defined by a curved proximal edge **68***c* proximate to the snorkel **32**, a curved distal edge **70***c* spaced from the proximal edge **68***c* by a pair of generally straight lateral edges **72***c*, **74***c* which are generally parallel to one another and have about the same length.

In the illustrated embodiment of FIGS. **16-20**, the blade **34***c* comprises a cutting tip **78***c*. The cutting tip **78***c* preferably includes cutting edges formed on selected portions of the distal edge **70***c* and adjacent portions of the lateral edges **72***c*, **74***c* for cutting through the trabecular meshwork for placement of the snorkel **32**. The cutting edges are sharp edges of beveled or tapered surfaces as discussed above in reference to FIG. **9**. The embodiment of FIGS. **16-20** may be efficaciously modified to incorporate the snorkel configuration of the embodiments of FIGS. **14** and **15**.

FIGS. **21-25** show different views of a self-trephining glaucoma stent device **30***d* having features and advantages in accordance with one embodiment. The stent **30***d* is generally similar to the stent **30** of FIGS. **3-9** except that it has a modified blade configuration. The stent **30***d* comprises a blade **34***d* which is a generally curved elongated sheet- or plate-like structure with an upper curved surface **62***d* and a lower curved surface **64***d* which defines a trough or open face channel **66***d*. The perimeter of the blade **34***d* is generally defined by a curved proximal edge **68***d* proximate to the snorkel **32**, a pair of inwardly converging curved distal edges **70***d*', **70***d*" spaced from the proximal edge **68***d* by a pair of generally straight respective lateral edges **72***d*, **74***d* which are generally parallel to one another and have about the same length. The distal edges **70***d*', **70***d*" intersect at a distal-most point **76***d* of the blade **34***d* proximate a blade cutting tip **78***d*.

In the illustrated embodiment of FIGS. **21-25**, the cutting tip **78***d* preferably includes cutting edges formed on the distal edges **70***d*', **70***d*" and extending from the distal-most point **76***d* of the blade **34***d*. In one embodiment, the cutting edges extend along only a portion of respective distal edges **70***d*', **70***d*." In another embodiment, the cutting edges extend along substantially the entire length of respective distal edges **70***d*', **70***d*." In yet another embodiment, at least portions of the lateral edges **72***d*, **74***d* proximate to respective distal edges **70***d*', **70***d*" have cutting edges. In a further embodiment, the tip **78***d* proximate to the distal-most end **76***d* is curved slightly inwards, as indicated generally by the arrow **88***d* in FIG. **21** and arrow **88***d* (pointed perpendicular and into the plane of the paper) in FIG. **22**, relative to the adjacent curvature of the blade **34***d*.

In the embodiment of FIGS. **21-25**, the cutting edges are sharp edges of beveled or tapered surfaces as discussed above in reference to FIG. **9**. The embodiment of FIGS. **21-25** may be efficaciously modified to incorporate the snorkel configuration of the embodiments of FIGS. **14** and **15**.

FIGS. **26-28** show different views of a self-trephining glaucoma stent device **30***e* having features and advantages in accordance with one embodiment. The stent device **30***e* generally comprises a snorkel **32***e* mechanically connected to or in mechanical communication with a blade or cutting tip **34***e*. The snorkel **32***e* has a seat, head or cap portion **38***e* mechanically connected to or in mechanical communication with a shank **40***e*, as discussed above. The shank **40***e* has a distal end or base **47***e*. The snorkel **32***e* further has a lumen **42***e*, which bifurcates into a pair of outlet channels **45***e*, as discussed above in connection with FIGS. **14** and **15**. Other lumen and inlet and outlet port configurations as taught or suggested herein may also be efficaciously used, as needed or desired.

In the illustrated embodiment of FIGS. **26-28**, the blade **34***e* extends downwardly and outwardly from the shank distal end **47***e*. The blade **34***e* is angled relative to a generally longitudinal axis **43***e* of the snorkel **32***e*, as best seen in FIGS. **27** and **28**. The blade **34***e* has a distal-most point **76***e*. The blade or cutting tip **34***e* has a pair of side edges **70***e*', **70***e*," including cutting edges, terminating at the distal-most point **76***e*, as best seen in FIG. **26**. In one embodiment, the cutting edges are sharp edges of beveled or tapered surfaces as discussed above in reference to FIG. **9**.

Referring to FIGS. **26-28**, in one embodiment, the blade **34***e* includes cutting edges formed on the edges **70***e*', **70***e*" and extending from the distal-most point **76***e* of the blade **34***d*. In one embodiment, the cutting edges extend along only a portion of respective distal edges **70***e*', **70***e*." In another embodiment, the cutting edges extend along substantially the entire length of respective distal edges **70***e*', **70***e*." In yet another embodiment, the blade or cutting tip **34***e* comprises a bent tip of needle, for example, a 30 gauge needle.

In general, any of the blade configurations disclosed herein may be used in conjunction with any of the snorkel configurations disclosed herein or incorporated by reference herein to provide a self-trephining glaucoma stent device for making an incision in the trabecular meshwork for receiving the corresponding snorkel to provide a pathway for aqueous outflow from the eye anterior chamber to Schlemm's canal, thereby effectively lowering and/or balancing the intraocular pressure (IOP). The self-trephining ability of the device, advantageously, allows for a "one-step" procedure in which the incision and placement of the snorkel are accomplished by a single device and operation. In any of the embodiments, fiducial markings or indicia, and/or preselected configuration of the snorkel seat, and/or positioning of the stent device in a preloaded applicator may be used for proper orientation and alignment of the device during implantation.

In many cases, a surgeon works from a temporal incision when performing cataract or goniometry surgery. FIG. **29** illustrates a temporal implant procedure, wherein a delivery apparatus or "applicator" **100** having a curved tip **102** is used to deliver a stent **30** to a temporal side **27** of the eye **10**. An incision **28** is made in the cornea **10**, as discussed above. The apparatus **100** is then used to introduce the stent **30** through the incision **28** and implant it within the eye **10**.

Still referring in particular to FIG. **29**, in one embodiment, a similarly curved instrument would be used to make the incision through the trabecular meshwork **21**. In other

embodiments, a self-trephining stent device **30** may be used to make this incision through the trabecular meshwork **21**, as discussed above. The temporal implantation procedure illustrated in FIG. **29** may be employed with the any of the various stent embodiments taught or suggested herein.

FIG. **30** illustrates one embodiment of an apparatus comprising an articulating stent applicator or retrieval device **100***a*. In this embodiment, a proximal arm **106** is attached to a distal arm **108** at a joint **112**. This joint **112** is movable such that an angle formed between the proximal arm **106** and the distal arm **108** can change. One or more claws **114** can extend from the distal arm **108**, in the case of a stent retrieval device. Similarly, this articulation mechanism may be used for the trabecular stent applicator, and thus the articulating applicator or retrieval device **100***a* may be either an applicator for the trabecular stent, a retrieval device, or both, in various embodiments. The embodiment of FIG. **30** may be employed with the any of the various stent embodiments taught or suggested herein.

FIG. **31** shows another illustrative method for placing any of the various stent embodiments taught or suggested herein at the implant site within the eye **10**. A delivery apparatus **100***b* generally comprises a syringe portion **116** and a cannula portion **118**. The distal section of the cannula **118** has at least one irrigating hole **120** and a distal space **122** for holding the stent device **30**. The proximal end **124** of the lumen of the distal space **122** is sealed from the remaining lumen of the cannula portion **118**. The delivery apparatus of FIG. **30** may be employed with the any of the various stent embodiments taught or suggested herein.

In one aspect of the invention, a delivery apparatus (or "applicator") is used for placing a trabecular stent through a trabecular meshwork of an eye. Certain embodiments of such a delivery apparatus are disclosed in copending U.S. application Ser. No. 10/101,548, filed Mar. 18, 2002, entitled APPLICATOR AND METHODS FOR PLACING A TRABECULAR SHUNT FOR GLAUCOMA TREATMENT, and U.S. Provisional Application No. 60/276,609, filed Mar. 16, 2001, entitled APPLICATOR AND METHODS FOR PLACING A TRABECULAR SHUNT FOR GLAUCOMA TREATMENT, the entire contents of each one of which are hereby incorporated by reference herein.

The stent has an inlet section and an outlet section. The delivery apparatus includes a handpiece, an elongate tip, a holder and an actuator. The handpiece has a distal end and a proximal end. The elongate tip is connected to the distal end of the handpiece. The elongate tip has a distal portion and is configured to be placed through a corneal incision and into an anterior chamber of the eye. The holder is attached to the distal portion of the elongate tip. The holder is configured to hold and release the inlet section of the trabecular stent. The actuator is on the handpiece and actuates the holder to release the inlet section of the trabecular stent from the holder. When the trabecular stent is deployed from the delivery apparatus into the eye, the outlet section is positioned in substantially opposite directions inside Schlemm's canal. In one embodiment, a deployment mechanism within the delivery apparatus includes a push-pull type plunger.

In some embodiments, the holder comprises a clamp. In some embodiments, the apparatus further comprises a spring within the handpiece that is configured to be loaded when the stent is being held by the holder, the spring being at least partially unloaded upon actuating the actuator, allowing for release of the stent from the holder.

In various embodiments, the clamp comprises a plurality of claws configured to exert a clamping force onto the inlet section of the stent. The holder may also comprise a plurality of flanges.

In some embodiments, the distal portion of the elongate tip is made of a flexible material. This can be a flexible wire. The distal portion can have a deflection range, preferably of about 45 degrees from the long axis of the handpiece.

The delivery apparatus can further comprise an irrigation port in the elongate tip.

Some aspects include a method of placing a trabecular stent through a trabecular meshwork of an eye, the stent having an inlet section and an outlet section, including advancing a delivery apparatus holding the trabecular stent through an anterior chamber of the eye and into the trabecular meshwork, placing part of the stent through the trabecular meshwork and into a Schlemm's canal of the eye; and releasing the stent from the delivery apparatus.

In various embodiments, the method includes using a delivery apparatus that comprises a handpiece having a distal end and a proximal end; an elongate tip connected to the distal end of the handpiece, the elongate tip having a distal portion and being configured to be placed through a corneal incision and into an anterior chamber of the eye; a holder attached to the distal portion of the elongate tip, the holder configured to hold and release the inlet section of the trabecular stent; and an actuator on the handpiece that actuates the holder to release the inlet section of the trabecular stent from the holder.

In one aspect, the trabecular stent is removably attached to a delivery apparatus (also known as "applicator"). When the trabecular stent is deployed from the delivery apparatus into the eye, the outlet section is positioned in substantially opposite directions inside Schlemm's canal. In one embodiment, a deployment mechanism within the delivery apparatus includes a push-pull type plunger. In some embodiments, the delivery applicator may be a guidewire, an expandable basket, an inflatable balloon, or the like.

Screw/Barb Anchored Stent

FIGS. **32** and **33** illustrate a glaucoma stent device **30***f* having features and advantages in accordance with one embodiment. This embodiment of the trabecular stent **30***f* includes a barbed or threaded screw-like extension or pin **126** with barbs **128** for anchoring. The barbed pin **126** extends from a distal or base portion **130** of the stent **30***f*.

In use, the stent **30***f* (FIG. **32**) is advanced through the trabecular meshwork **21** and across Schlemm's canal **22**. The barbed (or threaded) extension **126** penetrates into the back wall **92** of Schlemm's canal **22** up to the shoulder or base **130** that then rests on the back wall **92** of the canal **22**. The combination of a shoulder **130** and a barbed pin **126** of a particular length limits the penetration depth of the barbed pin **126** to a predetermined or preselected distance. In one embodiment, the length of the pin **126** is about 0.5 mm or less. Advantageously, this barbed configuration provides a secure anchoring of the stent **30***f*. As discussed above, correct orientation of the stent **30***f* is ensured by appropriate fiducial marks, indicia or the like and by positioning of the stent in a preloaded applicator.

Referring to FIG. **32**, the aqueous flows from the anterior chamber **20**, through the lumen **42***f*, then out through two side-ports **56***f* to be directed in both directions along Schlemm's canal **22**. Alternatively, flow could be directed in only one direction through a single side-port **56***f*. In other embodiments, more then two outlet ports **56***f*, for example, six to eight ports (like a pin wheel configuration), may be efficaciously used, as needed or desired.

Still referring to FIG. **32**, in one embodiment, the stent **30***f* is inserted through a previously made incision in the trabecular meshwork **21**. In other embodiments, the stent **30***f* may be combined with any of the blade configurations taught or suggested herein to provide self-trephining capability. In these cases, the incision through the trabecular meshwork **21** is made by the self-trephining stent device that has a blade at its base or proximate to the base.

Deeply Threaded Stent

FIG. **34** illustrates a glaucoma stent device **30***g* having features and advantages in accordance with one embodiment. The stent **30***g* has a head or seat **38***g* and a shank or main body portion **40***g* with a base or distal end **132**. This embodiment of the trabecular stent **30***g* includes a deep thread **134** (with threads **136**) on the main body **40***g* of the stent **30***g* below the head **38***g*. The threads may or may not extend all the way to the base **132**.

In use, the stent **30***g* (FIG. **34**) is advanced through the meshwork **21** through a rotating motion, as with a conventional screw. Advantageously, the deep threads **136** provide retention and stabilization of the stent **30***g* in the trabecular meshwork **21**.

Referring to FIG. **34**, the aqueous flows from the anterior chamber **20**, through the lumen **42***g*, then out through two side-ports **56***g* to be directed in both directions along Schlemm's canal **22**. Alternatively, flow could be directed in only one direction through a single side-port **56***g*. In other embodiments, more then two outlet ports **56***g* may be efficaciously used, as needed or desired.

One suitable applicator or delivery apparatus for this stent **30***g* (FIG. **34**) includes a preset rotation, for example, via a wound torsion spring or the like. The rotation is initiated by a release trigger on the applicator. A final twist of the applicator by the surgeon and observation of suitable fiducial marks, indicia or the like ensure proper alignment of the side ports **56***g* with Schlemm's canal **22**.

Referring to FIG. **34**, in one embodiment, the stent **30***g* is inserted through a previously made incision in the trabecular meshwork **21**. In other embodiments, the stent **30***g* may be combined with any of the blade configurations taught or suggested herein to provide self-trephining capability. In these cases, the incision through the trabecular meshwork **21** is made by the self-trephining stent device that has a blade at its base or proximate to the base.

Rivet Style Stent

FIG. **35** illustrates a glaucoma stent device **30***h* having features and advantages in accordance with one embodiment. The stent has a base or distal end **138**. This embodiment of the trabecular stent **30***h* has a pair of flexible ribs **140**. In the unused state, the ribs are initially generally straight (that is, extend in the general direction of arrow **142**).

Referring to FIG. **35**, upon insertion of the stent **30***h* through the trabecular meshwork **21**, the ends **144** of respective ribs **140** of the stent **30***h* come to rest on the back wall **92** of Schlemm's canal **22**. Further advancement of the stent **30***h* causes the ribs **140** to deform to the bent shape as shown in the drawing of FIG. **35**. The ribs **140** are designed to first buckle near the base **138** of the stent **30***h*. Then the buckling point moves up the ribs **140** as the shank part **40***h* of the stent **30***h* is further advanced through the trabecular meshwork **21**.

The lumen **42***h* (FIG. **35**) in the stent **30***h* is a simple straight hole. The aqueous flows from the anterior chamber **20**, through the lumen **42***h*, then out around the ribs **140** to the collector channels further along Schlemm's canal **22** in either direction.

Referring to FIG. **35**, in one embodiment, the stent **30***h* is inserted through a previously made incision in the trabecular meshwork **21**. In other embodiments, the stent **30***h* may be combined with any of the blade configurations taught or suggested herein to provide self-trephining capability. In these cases, the incision through the trabecular meshwork **21** is made by the self-trephining stent device that has a blade at its base or proximate to the base.

Grommet Style Stent

FIG. **36** illustrates a glaucoma stent device **30***i* having features and advantages in accordance with one embodiment. This embodiment of the trabecular stent **30***i* includes a head or seat **38***i*, a tapered base portion **146** and an intermediate narrower waist portion or shank **40***i*.

In use, the stent **30***i* (FIG. **36**) is advanced through the trabecular meshwork **21** and the base **146** is pushed into Schlemm's canal **22**. The stent **30***i* is pushed slightly further, if necessary, until the meshwork **21** stretched by the tapered base **146** relaxes back and then contracts to engage the smaller diameter portion waist **40***i* of the stent **30***i*. Advantageously, the combination of the larger diameter head or seat **38***i* and base **146** of the stent **30***i* constrains undesirable stent movement. As discussed above, correct orientation of the stent **30***i* is ensured by appropriate fiducial marks, indicia or the like and by positioning of the stent in a preloaded applicator.

Referring to FIG. **36**, the aqueous flows from the anterior chamber **20**, through the lumen **42***i*, then out through two side-ports **56***i* to be directed in both directions along Schlemm's canal **22**. Alternatively, flow could be directed in only one direction through a single side-port **56***i*. In other embodiments, more then two outlet ports **56***i* may be efficaciously used, as needed or desired.

Still referring to FIG. **36**, in one embodiment, the stent **30***i* is inserted through a previously made incision in the trabecular meshwork **21**. In other embodiments, the stent **30***i* may be combined with any of the blade configurations taught or suggested herein to provide self-trephining capability. In these cases, the incision through the trabecular meshwork **21** is made by the self-trephining stent device, which has a blade at its base or proximate to the base.

Biointeractive Stent

FIG. **37** illustrates a glaucoma stent device **30***j* having features and advantages in accordance with one embodiment. This embodiment of the trabecular stent **30***j* utilizes a region of biointeractive material **148** that provides a site for the trabecular meshwork **21** to firmly grip the stent **30***j* by ingrowth of the tissue into the biointeractive material **148**. As shown in FIG. **37**, preferably the biointeractive layer **148** is applied to those surfaces of the stent **30***j*, which would abut against or come in contact with the trabecular meshwork **21**.

In one embodiment, the biointeractive layer **148** (FIG. **37**) may be a region of enhanced porosity with a growth promoting chemical. In one embodiment, a type of bio-glue **150** that dissolves over time is used to hold the stent secure during the time between insertion and sufficient ingrowth for stabilization. As discussed above, correct orientation of the stent **30***j* is ensured by appropriate fiducial marks, indicia or the like and by positioning of the stent in a preloaded applicator.

Referring to FIG. **37**, the aqueous flows from the anterior chamber **20**, through the lumen **42***j*, then out through two side-ports **56***j* to be directed in both directions along Schlemm's canal **22**. Alternatively, flow could be directed in only one direction through a single side-port **56***j*. In other embodiments, more then two outlet ports **56***j* may be efficaciously used, as needed or desired.

Still referring to FIG. **37**, in one embodiment, the stent **30***j* is inserted through a previously made incision in the trabecular meshwork **21**. In other embodiments, the stent **30***j* may be

combined with any of the blade configurations taught or suggested herein to provide self-trephining capability. In these cases, the incision through the trabecular meshwork **21** is made by the self-trephining stent device, which has a blade at its base or proximate to the base.

Glued or Welded Stent

FIG. **38** illustrates a glaucoma stent device **30***k* having features and advantages in accordance with one embodiment. This embodiment of the trabecular stent **30***k* is secured in place by using a permanent (non-dissolving) bio-glue **152** or a "welding" process (e.g., heat) to form a weld **152**. The stent **30***k* has a head or seat **38***k* and a lower surface **46***k*.

The stent **30***k* is advanced through the trabecular meshwork **21** until the head or seat **38***k* comes to rest on the trabecular meshwork **21**, that is, the head lower surface **46***k* abuts against the trabecular meshwork **21**, and the glue or weld **152** is applied or formed therebetween, as shown in FIG. **38**. As discussed above, correct orientation of the stent **30***k* is ensured by appropriate fiducial marks, indicia or the like and by positioning of the stent in a preloaded applicator.

Referring to FIG. **38**, the aqueous flows from the anterior chamber **20**, through the lumen **42***k*, then out through two side-ports **56***k* to be directed in both directions along Schlemm's canal **22**. Alternatively, flow could be directed in only one direction through a single side-port **56***k*. In other embodiments, more then two outlet ports **56***k* may be efficaciously used, as needed or desired.

Still referring to FIG. **38**, in one embodiment, the stent **30***k* is inserted through a previously made incision in the trabecular meshwork **21**. In other embodiments, the stent **30***k* may be combined with any of the blade configurations taught or suggested herein to provide self-trephining capability. In these cases, the incision through the trabecular meshwork **21** is made by the self-trephining stent device, which has a blade at its base or proximate to the base.

Hydrophilic Latching Stent

FIG. **39** illustrates a glaucoma stent device **30***m* having features and advantages in accordance with one embodiment. This embodiment of the trabecular stent **30***m* is fabricated from a hydrophilic material that expands with absorption of water. Desirably, this would enable the device **30***m* to be inserted through a smaller incision in the trabecular meshwork **21**. The subsequent expansion (illustrated by the smaller arrows **154**) of the stent **30***m* would advantageously enable it to latch in place in the trabecular meshwork **21**. As discussed above, correct orientation of the stent **30***m* is ensured by appropriate fiducial marks, indicia or the like and by positioning of the stent in a preloaded applicator.

Referring to FIG. **39**, the aqueous flows from the anterior chamber **20**, through the lumen **42***m*, then out through two side-ports **56***m* to be directed in both directions along Schlemm's canal **22**. Alternatively, flow could be directed in only one direction through a single side-port **56***m*. In other embodiments, more then two outlet ports **56***m* may be efficaciously used, as needed or desired.

Still referring to FIG. **39**, in one embodiment, the stent **30***m* is inserted through a previously made incision in the trabecular meshwork **21**. In other embodiments, the stent **30***m* may be combined with any of the blade configurations taught or suggested herein to provide self-trephining capability. In these cases, the incision through the trabecular meshwork **21** is made by the self-trephining stent device, which has a blade at its base or proximate to the base.

Photodynamic Stent

FIG. **40** illustrates a glaucoma stent device **30***n* having features and advantages in accordance with one embodiment. This embodiment of the trabecular stent **30***n* is fabricated from a photodynamic material that expands on exposure to light.

It is commonly known that there is a diurnal variation in the aqueous humor production by the eye—it is higher during the day than it is at night. The lumen **42***n* of the stent **30***n* responds to light entering the cornea during the day by expanding and allowing higher flow of aqueous through the lumen **42***n* and into Schlemm's canal **22**. This expansion is generally indicated by the smaller arrows **156** (FIG. **40**) which show the lumen **42***n* (and ports) expanding or opening in response to light stimulus. (The light or radiation energy E is generally given by $E=h\nu$, where h is Planck's constant and ν is the frequency of the light provided.) At night, in darkness, the lumen diameter decreases and reduces the flow allowed through the lumen **42***n*. In one embodiment, an excitation wavelength that is different from that commonly encountered is provided on an as-needed basis to provide higher flow of aqueous to Schlemm's canal **22**.

This photodynamic implementation is shown in FIG. **40** for the self-latching style of stent **30***n*, but can be efficaciously used with any of the other stent embodiments, as needed or desired. As discussed above, correct orientation of the stent **30***n* is ensured by appropriate fiducial marks, indicia or the like and by positioning of the stent in a preloaded applicator.

Referring to FIG. **40**, the aqueous flows from the anterior chamber **20**, through the lumen **42***n*, then out through two side-ports **56***n* to be directed in both directions along Schlemm's canal **22**. Alternatively, flow could be directed in only one direction through a single side-port **56***n*. In other embodiments, more then two outlet ports **56***n* may be efficaciously used, as needed or desired.

Still referring to FIG. **40**, in one embodiment, the stent **30***n* is inserted through a previously made incision in the trabecular meshwork **21**. In other embodiments, the stent **30***n* may be combined with any of the blade configurations taught or suggested herein to provide self-trephining capability. In these cases, the incision through the trabecular meshwork **21** is made by the self-trephining stent device, which has a blade at its base or proximate to the base.

Collector Channel Alignment Stent

FIG. **41** illustrates a glaucoma stent device **30***p* having features and advantages in accordance with one embodiment. This figure depicts an embodiment of a stent **30***p* that directs aqueous from the anterior chamber **20** directly into a collector channel **29**, which empties into aqueous veins. The stent **30***p* has a base or distal end **160**.

In the illustrated embodiment of FIG. **41**, a removable alignment pin **158** is utilized to align the stent lumen **42***p* with the collector channel **29**. In use, the pin **158** extends through the stent lumen **42***p* and protrudes through the base **160** and extends into the collector channel **29** to center and/or align the stent **30***p* over the collector channel **29**. The stent **30***p* is then pressed firmly against the back wall **92** of Schlemm's canal **22**. A permanent bio-glue **162** is used between the stent base and the back wall **92** of Schlemm's canal **22** to seat and securely hold the stent **30***p* in place. Once positioned, the pin **158** is withdrawn from the lumen **42***p* to allow the aqueous to flow directly from the anterior chamber **20** into the collector duct **29**. The collector ducts are nominally 20 to 100 micrometers (μm) in diameter and are visualized with a suitable microscopy method (such as ultrasound biomicroscopy (UBM)) or laser imaging to provide guidance for placement of the stent **30***p*.

Referring to FIG. **41**, in one embodiment, the stent **30***p* is inserted through a previously made incision in the trabecular meshwork **21**. In other embodiments, the stent **30***p* may be

combined with any of the blade configurations taught or suggested herein to provide self-trephining capability. In these cases, the incision through the trabecular meshwork **21** is made by the self-trephining stent device, which has a blade at its base or proximate to the base.

Barbed Stent (Anterior Chamber to Collector Channel)

FIG. **42** illustrates a glaucoma stent device **30***q* having features and advantages in accordance with one embodiment. This figure depicts an embodiment of a stent **30***q* that directs aqueous from the anterior chamber **20** directly into a collector channel **29**, which empties into aqueous veins. The stent **30***q* has a base or distal end **166** and the channel **29** has wall(s) **164**.

In the illustrated embodiment of FIG. **42**, a barbed, small-diameter extension or pin **168** on the stent base **166** is guided into the collector channel **29** and anchors on the wall(s) **164** of the channel **29**. The pin **168** has barbs **170** which advantageously provide anchoring of the stent **30***q*. The collector ducts **29** are nominally 20 to 100 micrometers (μm) in diameter and are visualized with a suitable microscopy method (such as ultrasound biomicroscopy (UBM)) or laser imaging to provide guidance for placement of the stent.

Referring to FIG. **42**, in one embodiment, the stent **30***q* is inserted through a previously made incision in the trabecular meshwork **21**. In other embodiments, the stent **30***q* may be combined with any of the blade configurations taught or suggested herein to provide self-trephining capability. In these cases, the incision through the trabecular meshwork **21** is made by the self-trephining stent device, which has a blade at its base or proximate to the base.

Valved Tube Stent (Anterior Chamber to Choroid)

FIG. **43** illustrates a valved tube stent device **30***r* having features and advantages in accordance with one embodiment. This is an embodiment of a stent **30***r* that provides a channel for flow between the anterior chamber **20** and the highly vascular choroid **17**. Clinically, the choroid **17** can be at pressures lower than those desired for the eye **10**. Therefore, this stent **30***r* includes a valve with an opening pressure equal to the desired pressure difference between the choroid **17** and the anterior chamber **10** or a constriction that provide the desired pressure drop.

Osmotic Membrane (Anterior Chamber to Choroid)

FIG. **44** illustrates an osmotic membrane device **30***s* having features and advantages in accordance with one embodiment. This embodiment provides a channel for flow between the anterior chamber **20** and the highly vascular choroid **17**. The osmotic membrane **30***s* is used to replace a portion of the endothelial layer of the choroid **17**. Since the choroid **17** is highly vascular with blood vessels, the concentration of water on the choroid side is lower than in the anterior chamber **20** of the eye **10**. Therefore, the osmotic gradient drives water from the anterior chamber **20** into the choroid **17**.

Clinically, the choroid **17** (FIG. **44**) can be at pressures lower than those desired for the eye **10**. Therefore, desirably, both osmotic pressure and the physical pressure gradient are in favor of flow into the choroid **17**. Flow control is provided by proper sizing of the area of the membrane; the larger the membrane area is the larger the flow rate will be. This advantageously enables tailoring to tune the flow to the desired physiological rates.

Ab Externo Insertion of Stent Via Small Puncture

FIG. **45** illustrates the implantation of a stent **30***t* using an ab externo procedure having features and advantages in accordance with one embodiment. In the ab externo procedure of FIG. **45**, the stent **30***t* is inserted into Schlemm's canal **21** with the aid of an applicator or delivery apparatus **100***c* that creates a small puncture into the eye **10** from outside.

Referring to FIG. **45**, the stent **30***t* is housed in the applicator **100***c*, and pushed out of the applicator **100***c* once the applicator tip is in position within the trabecular meshwork **21**. Since the tissue surrounding the trabecular meshwork **21** is optically opaque, an imaging technique, such as ultrasound biomicroscopy (UBM) or a laser imaging technique, is utilized. The imaging provides guidance for the insertion of the applicator tip and the deployment of the stent **30***t*. This technique can be used with a large variety of stent embodiments with slight modifications since the trabecular meshwork **21** is punctured from the scleral side rather than the anterior chamber side in the ab externo insertion.

FIG. **46** a glaucoma stent device **30***u* having features and advantages in accordance with a modified embodiment. This grommet-style stent **30***u* for ab externo insertion is a modification of the embodiment of FIG. **36**. In the embodiment of FIG. **46**, the upper part or head **38***u* is tapered while the lower part or base **172** is flat, as opposed to the embodiment of FIG. **36**. The stent **30***u* is inserted from the outside of the eye **10** through a puncture in the sclera. Many of the other embodiments of stents taught or suggested herein can be modified for similar implantation.

This ultra microscopic device **30***u* (FIG. **46**) can be used with (1) a targeting Lasik-type laser, or with (2) contact on eyes or with (3) combined ultrasound microscope or (4) other device inserter handpiece.

Targeted Drug Delivery to the Trabecular Meshwork

FIG. **47** illustrates a targeted drug delivery implant **30***v* having features and advantages in accordance with one embodiment. This drawing is a depiction of a targeted drug delivery concept. The slow release implant **30***v* is implanted within the trabecular meshwork **21**.

A drug that is designed to target the trabecular meshwork **21** to increase its porosity, or improve the active transport across the endothelial layer of Schlemm's canal **22** can be stored in this small implant **30***v* (FIG. **47**). Advantageously, slow release of the drug promotes the desired physiology at minimal dosage levels since the drug is released into the very structure that it is designed to modify.

Dose Response

The programmed (also know as "Targeted") stent placement refers to the intentional placement of a stent or stents at a particular location or locations in Schlemm's canal for the purpose of providing a benefit in the form of more optimal outflow. For example, a method can be provided which includes assessing the aqueous flow characteristics of an eye. Such characteristics can include, for example, but without limitation, collector channel distribution, collector channel flow characteristics, outflow resistance, outflow capacity, shape/size/tortuosity of Schlemm's canal, and other factors). The method can also include determining an optimal stent placement and implanting stents in one or plurality of positions and procedures. For example, the determination of the desired stent placement can include consideration of a database of cadaver anatomy regarding the number and location of collector channels, the patient's micro-anatomy data, the number of stents to be used, the type of stents to be used, the location of any previously implanted stents whether the desired stent is drug-loaded, gene-loaded or surface treated, and/or any associated drug therapy.

FIG. **48** includes a flow diagram illustrating a decision tree for determining desired stent placement. In the illustrated embodiment, after it is determined that a patient is suffering from excess of intraocular pressure (IOP), a bypass flow model is determined to aid in the decision of whether or not to use single or multiple stents. Optionally, the configuration of collector channels in the patient's eye can be met to aid in the

creation of a bypass flow model. Further, other information can be used, such as, for example, but without limitation, outflow resistance, aqueous production, and venous pressure.

The bypass flow model, which can be based on the above-noted information, is determined so as to provide a desired strategy for lowering the excessive intraocular pressure. If it is decided that a single stent should be used, an optimized stent location is first determined based on the bypass flow model. The implantation of the single stent results in reduced IOP. After this implantation, it is again determined if there is a need for further reduction in IOP. If additional IOP reduction is desired, then a further bypass flow model is created. For example, the second bypass flow model can be determined in the same or similar manner as the first bypass flow model described above. In light of the second bypass flow model, an additional stent can be implanted at an optimized location to further reduce IOP.

If it is determined, in light of the first bypass flow model, that multiple stents should be used, the location of the multiple stents is first optimized. Then, the multiple stents are implanted. Afterwards, it is again determined if additional intraocular pressure reduction is needed, and the trimming can continue as noted above.

Where additional stents are implanted in light of the second bypass flow model, the additional stents can be different from the first stents implanted. For example, where single or multiple stents are implanted in accordance with the first bypass flow model, the additional stents can be of a different type. For example, in one embodiment, the first stent is a G1 (First generation) trabecular stent that has been disclosed in copending applications and the second stent(s) is the same G1 trabecular stent. In another embodiment, the second stent(s) is different from the first stent; for example, the second stent is a G2 stent (that is, "injectable axisymmetric stent"; a second generation stent). In still another embodiment, the second stent(s) is smaller than (in some case, larger than) the first stent. The dose response may also relate to the stent configuration or characteristics such as drug-loading or surface treatment enabling enhancing aqueous transport or therapeutic effects on the tissue as needed. Drug-loaded or drug-eluting stent may comprise different types of drugs including, but not limited to, those cited in copending patent application Ser. No. 10/046,137 filed Nov. 8, 2001, entitled DRUG RELEASING TRABECULAR IMPLANT FOR GLAUCOMA TREATMENT, the entire contents of which is hereby incorporated by reference.

With reference to FIG. **49**A, a stent extending between an anterior chamber **20** of an eye, through the trabecular meshwork **21**, and into Schlemm's canal **22** of an eye can be configured to be axisymmetric with respect to the flow of aqueous therethrough. For example, as shown in FIG. **49**A, the stent **229**A comprises an inlet end **230** configured to be disposed in the anterior chamber **20**. The second end **231** of the stent **229**A is configured to be disposed in Schlemm's canal **22**.

At least one lumen **239** extends through the stent **229**A between the inlet and outlet ends **230**, **232**. The lumen **239** defines an opening **232** at the inlet end **230** as well as an outlet **233** at the outlet end **231**.

In the illustrated embodiment, an exterior surface **238** of the stent **229**A is cone-shaped. Thus, a circumference of the exterior surface **238** adjacent to the inlet end **230** is smaller than the circumference of the outer surface **238** at the outlet end **231**.

With the stent **229**A extending through the trabecular meshwork **21**, the tissue of the trabecular meshwork **221** provides additional anchoring force for retaining the stent **229**A with its inlet end **230** in the anterior chamber and its outlet end **231** in Schlemm's canal. For example, the trabecular meshwork **21** would naturally tend to close an aperture occupied by the stent **229**A. As such, the trabecular meshwork **221** would tend to squeeze the stent **229**A. Because the exterior surface **238** is conical, the squeezing force applied by the trabecular meshwork **221** would tend to draw the stent **229**A towards Schlemm's canal **22**. In the illustrated embodiment, the stent **229**A is sized such that a portion **234** of the stent **229** adjacent to the inlet end **230** remains in the anterior chamber **20** while a portion **235** of the stent **229** adjacent to the outlet end **231** remains in Schlemm's canal **22**.

In the illustrated embodiment, the outer surface **238** of the stent **229**A is straight. Alternatively, the outer surface **238** can have other contours such as, for example, but without limitation curved or stepped. In one embodiment, the outer surface **238** can be curved in a concave manner so as to produce a trumpet-like shape. Alternatively, the outer surface **238** can be convex.

The stent **229**A preferably includes one or plurality of posts or legs **236** configured to maintain a space between the outlet opening **233** and a wall of Schlemm's canal **22**. As such, the legs **236** prevent a wall of Schlemm's canal from completely closing off the outlet opening **233** of the stent **229**A. In the illustrated embodiment, the legs **236** are coupled to the distal-most surface of the stent **229**A and are substantially parallel to an implant axis extending through the stent **229**A and between the anterior chamber **20** and Schlemm's canal **22**.

This arrangement of the legs **236** and the outlet **233** imparts an axisymmetric flow characteristic to the stent **229**A. For example, aqueous can flow from the outlet **233** in any direction. Thus, the stent **229**A can be implanted into Schlemm's canal at any angular position relative to its implant axis. Thus, it is not necessary to determine the angular orientation of the stent **229**A prior to implantation, nor is it necessary to preserve a particular orientation during an implantation procedure.

FIG. **49**B illustrates a modification of the stent **229**A, identified generally by the reference numeral **229**B. In this embodiment, the stent **229**B includes a flange **237** extending radially from the portion **234**. Preferably, the flange **237** is configured to retain the first portion **234** within the anterior chamber **20**. It is to be recognized that although generally, aqueous will flow from the anterior chamber **20** towards Schlemm's canal **22**, the stent **229**A, **229**B or any of the above-described stents as well as other stents described below, can provide for omni-directional flow of aqueous.

FIG. **49**C illustrates another modification of the stent **229**A, identified generally by the reference numeral **229**C. In this embodiment, the outer surface **238**C is not conical. Rather, the outer surface **238**C is cylindrical. The stent **229**C includes a flange **240** that can be the same size and shape as the flange **237**. The legs **236**C extend from the flange **240**.

Constructed as such, the natural tendency of the tissue of the trabecular meshwork **21** to close the hole in which the stent **229**C is disposed, aids in anchoring the stent **229**C in place. Additionally, the legs **236**C aid in preventing the walls of Schlemm's canal from completely closing the outlet **233**C of the lumen **239**C.

Device for Mechanically Distending Collector Duct

FIG. **50**A is an enlarged cross-sectional view of a portion of the eye **10** showing, anatomically, the trabecular meshwork **21**, Schlemm's canal **22**, and a collector duct **23** in a natural state. FIG. **50**B shows a stent **229**C extending into and thereby distending the collector duct **23**.

The collector duct **23** has an inner diameter identified generally by the reference numeral D_1, when in a relaxed or natural state. Because the collector duct **23** is not typically perfectly round, the diameter D_1 can correspond to an "equivalent" diameter. As used herein, the equivalent diameter can be determined by dividing the circumference of the inner surface of the collector duct **23** by π.

The stent **229**D is sized to extend from the anterior chamber **20** and into the collector duct **23**. Thus, in the illustrated embodiment, the stent **229**D includes an upstream end portion **230**D and a downstream end portion **243**.

The upstream portion **230**D is configured to open into the anterior chamber **20**. The stent **229**D is sized so as to extend from the anterior chamber **20** and into the collector duct **23**. In the illustrated embodiment, the stent **229**D is sized so as to extend from the anterior chamber **20**, through the trabecular meshwork **21**, through a portion of Schlemm's canal **22**, and into the collector duct **23**. However, it is conceived that the stent **229**D could bypass Schlemm's canal **22** and extend directly into a portion of the collector duct **23** downstream from Schlemm's canal **22**.

The downstream end portion **243** can have an outer diameter D_2 that is larger that the diameter D_1. Preferably, the end portion **243** is sized and configured for easy insertion into a collect duct **23** without injuring the tissue or tissue surface of the collector duct **23**. Thus, when the end portion **243** is disposed in the collector duct **23**, the collector duct **23** is distended, i.e., enlarged. As such, the resistance against the outflow of aqueous provided by the collector duct **23** in its natural state can be reduced, thereby reducing IOP.

Preferably, the end portion **243** has a diameter D_2 substantially larger than the equivalent diameter D_1 of the duct **23** so as to deform the collector duct beyond its elastic threshold into plastic deformation region. As such, the collector duct **23** can aid in anchoring the stent **229**D in place.

Applicator for Multiple Stent Implantation

FIG. **51**A is a perspective view of a stent delivery applicator **201** configured for multiple stent deployment. The delivery applicator **201** comprises an injection sheath **246** defining a stent lumen **249**, a distal stent-holding section **259**, and a handle **205**.

The handle **205** includes an outer surface preferably configured to be grasped by a human hand. Additionally, the handle can comprise a stent delivery button **203**. By way of example, the stent delivery button **203** is configured to cause a stent discharge mechanism to discharge, from the applicator sheath **246**, one stent at a time. The applicator **201** can be configured to store and discharge a plurality of any combination of the stents **229**, **30**, **30***a*, **30***b*, **30***c*, **30***d*, **30***e*, **30***f*, **30***g*, **30***h*, **30***i*, **30***j*, **30***k*, **30***m*, **30***n*, **30***p*, **30***q*, **30***r*, **30***s*, **30***t*, **30***u*, **30***v*, **229**A, **229**B, **229**C, and **229**D described above, the additional stents described below, or any other ocular stent or implant. In the illustrated embodiment, the applicator **201** is loaded with a plurality of the stents **229**C

The applicator **201** can include other features as well, for example, but without limitation, an optional connector **209** for connecting to an external ultrasound power source, a fluid infusing port **204** for fluid infusion or viscocanalostomy, and a steering mechanism control device **202** configured to control the steering of a steerable section **251** of the applicator **201**.

The steerable section **251** can be configured to deflect the distal stent-holding section **259** about at least one axis. Optionally, the steerable section **251** can configured to deflect the distal stent-holding section **259** about at least two axes, one axis being substantially perpendicular to the other. Thus, the portion of the sheath **246** that defines part of the steerable section **251** is flexible. Generally, similar steering mechanisms for deflecting a portion of an medical device, such as endoscopes, are well-known in the art.

With reference to FIG. **51**B, in the illustrated embodiment, the steering actuator **202** is connected to a plurality of pulling wires **256**A, **256**B. The wires **256**A, **256**B have distal portions **253**A, **253**B, respectively, disposed distally from the handle **205**. The end **252**A of the distal wire portion **253**A of the first pulling wire **256**A is attached to one side of an inner surface of the sheath **246**. The second pulling wire **256**B has its end **252**B of the distal wire portion **253**B attached to the opposite side of the inner surface of the sheath **246**. The wire ends **252**A and **252**B are disposed within the steerable distal section **251**.

With reference to FIG. **51**C, a relatively rigid guide **254** is disposed in the lumen at an appropriate location proximal to the wire ends **252**A, **252**B. The guide is configured to guide the pull wires **256**A, **256**B such that the sheath **246** is deflected when the pull wires **256**A, **256**B are pulled. In the illustrated embodiment, the guide **254** is in the form of a plate member.

The guide **254** can include holes **255**A, **255**B through which the pulling wires **253**A, **253**B extend. The guide **254** and the points at which the wire ends **252**A, **25**B are spaced. As such, when the pull wires **253**A, **253**B are pulled by actuation of the steering actuator **202**, the distal end of the sheath **246** is deflected. For example, as shown in FIG. **51**D, when the wire **256**A is pulled, the sheath deflects from Position I to Position II.

As noted above, the delivery apparatus **201** can be configured to discharge a plurality of stents, one at a time, for implantation. In the illustrated embodiment, as shown in FIG. **51**B, the delivery apparatus **201** includes a plunger **244** connected with the stent delivery button **203**. The plunger **244** can comprise one or a plurality of plunger bodies that are joined at the distal plunger end **244**B. The distal plunger end **244**B has a generally round configuration and smooth surface adapted for evenly pushing a stent, such as the stent **229**C, out of the sheath during a deployment phase of an implantation procedure.

As noted above, the sheath **246** defines a lumen **249** having a plunger **244**. A space between the plunger **244** and the distal end **242** is reserved for storing a plurality of stents. The sheath **246** includes at least one holding member **245** for each stent **229**C stored therein. The holding members **245** are configured to retain the stents **229**C in place during storage and use, and to allow the stents **229**C to pass when the stent **229**C is pushed by the plunger **244**.

In the illustrated embodiment, the sheath **146** includes a row of a plurality of holding members **245** upstream and downstream from each stent **229**C stored in the sheath **246**. Thus, each stent **229**C is prevented from unintentionally moving in the upstream and downstream directions.

FIG. **51**B illustrates two stents **229**C being stored in the sheath **246**. However, it is conceived that the sheath **246** and holding members **245** can be configured to hold one, three, or more stents **229**C within the stent-holding distal end **259**.

The holding member **245** can be a wire configured to exerted a force to hold the stents **229**C in place during storage and use, until the plunger **244** is moved to discharge a stent **229**C from the end **242**. For example, the wire can be made from a spring metal, an elastically deformable plastic, or other material, sized and shaped to retain the stents **229**C during storage, and to allow the stents **229**C to pass under a force that can be generated by or applied to the plunger **244**, toward the end **242**. In the illustrated embodiment, the wires forming the holding members **245** extend generally parallel

to and convexly into the lumen **249**, and thus define stops for preventing unintentional movement of the stents **229**C.

Alternatively, the holding members **245** can be in the form of a mechanically or electronically actuatable gate. Such a gate can be configured to move from a closed position in which the stents **229**C are retained in the storage positions, and an open position in which the stents **229**C can be moved in the downstream direction. A mechanical gate can be formed from members that can be moved or deflected radially from the inner surface of the lumen **249**, under the control of a pull wire (not shown). An electronic gate can also include radially moveable or deflectable members controlled by an electronic actuator, such as, for example, but without limitation, solenoids, stepper motors, servo motors, and piezoelectric modules.

Alternatively, piezoelectric modules can be used to form the holding members. For example, small piezoelectric modules can be mounted on the inner surface of the sheath **246** to form stops when in a locked position. The piezoelectric modules can be connected to a power supply with conduits. Thus, when actuated, the piezoelectric modules can contract so as to move to an open position in which the stents **229**C can pass.

As noted above, the applicator **201** preferably is configured to eject one stent at a time from the end **242**. Thus, the applicator **201** can be configured to move the plunger **244** a predetermined distance each time the button **203** is depressed. For example, the button can be mechanically connected to the plunger **244** so as to move the plunger **244** downstream through the sheath **246** over the predetermined distance. The predetermined distance can be, for example, equal to about the length of the stent **229**C.

Alternatively, the plunger can be driven by an electronic actuator (not shown) configured to eject one stent **229**C at a time from the sheath **246**. For example, the electronic actuator can be configured to drive the plunger **244** over the predetermined distance each time the button **203** is depressed. The electronic actuator can be, for example but without limitation, solenoids, stepper motors, servo motors, and piezoelectric modules. Driver electronics (not shown) can be configured to drive the actuator so as to urge the plunger **244** over the predetermined distance.

Preferably, the end **242** of the sheath **246** is sharpened to define a cutting (microtrephining) tip for creating a hole within the trabecular meshwork **21** for stent placement. Thus, the applicator **201** can be used for cutting the trabecular meshwork **21** and for implanting stents.

A further advantage is provided where the applicator includes an illumination feature for illuminating at least a portion of the implantation site. For example, the illumination feature can be configured to generally illuminate the site at which a stent is to be implanted. Optionally, the illumination feature can be configured to generate a reticule for aligning the applicator with the desired implantation site. In one embodiment, a light source is provided to the tip section **242** of the stent applicator **201** wherein either laser light is provided for cutting/spotting or fiber optic light is provided for illumination.

For example, but without limitation, the illumination feature can comprise a small diameter light pipe or optic fiber element configured to emit a fine point or beam of light and configured to be introduced ab-internally. Additionally, the face or lens of the pipe or element can be configured to be placed against the trabecular meshwork. In one embodiment, the light pipe or optic fiber is the construct material of the sheath **246** of the stent delivery applicator **241**A for multiple stent deployment as shown in FIG. **51**B. In another embodiment, the light pipe or optic fiber is snugly inserted within the lumen **249** of the applicator sheath **246** or over the outer periphery of the applicator sheath **246**. Optionally, the illumination device can be configured such that the point or beam emitting from the light tube would be highly visible from the outside of the eye and serve to guide the implantation of a stent.

As an alternative to including an illumination feature with the applicator **201**, simple non-invasive trans-scleral illumination, if of the proper intensity and wavelength, perhaps in a darkened environment, could silhouette the Schlemm's canal, trabecular meshwork, or more probably, the scleral spur with sufficient resolution to enable ab-externo placement of a device into Schlemm's canal. In this case, blood could be backed up in a retrograde manner into Schlemm's canal by the surgeon to provide additional optical density. Imaging means for ab internally imaging the anatomic structures for TBS stent implantation using ultrasound imaging, laser imaging, OCT imaging or multi-wavelength scanning can also be provided.

A further advantage is provided where the applicator **201** also includes an imaging feature. For example, where the applicator **201** includes an imaging feature for transmitting a video representation of an implantation site of a stent to a user of the applicator, an implantation procedure can be further simplified. The imaging feature can utilize any type of known imaging techniques, including, for example, but without limitation, optical, and ultrasonic. In one embodiment, an endoscope is mounted at the tip section **242** of the stent applicator **201** for visualization during stent deployment and/or implantation.

FIG. **51**D shows one embodiment of the applicator **201** of FIG. **51**A having an ultrasonic imaging system. The illustrated embodiment of the imaging system is included on an applicator with a steerable section. However, it is to be noted that the imaging system can be used on an applicator that does not have a steerable section.

In one embodiment, the ultrasonic imaging system comprises two ultrasonic probes or transducers **206**, **207**. The transducers **206**, **207** can be formed from an ultrasound ring or ultrasound tape. Preferably, the transducers **206**, **207** are located adjacent to the distal end **242** of the delivery apparatus **201**. As such, the transducers **206**, **207** can move with the distal end **242** during an implantation procedure.

The ultrasonic transducers **206**, **207** are connected by flexible wires (not shown) through the interior void **243** of the apparatus or through within the sheath **246** to the connector **209** located at the handle **205** so that the ultrasonic signals are directed outwardly and received inwardly relative to the transducers **206**, **207**. For example, one of the transducers **206**, **207** can be configured to emit ultrasonic energy, and the other can be configured to absorb the reflected portion of the emitted ultrasonic energy and to produce a signal indicative of the absorbed energy.

In order to enhance the viewing and positioning of the distal end **242** of the apparatus, an ultrasonic marker **208**, which is visible to ultrasonic energy, can be mounted at about the distal end **242** of the applicator **201**. For example, but without limitation, such a marker **208** can be in the form of one or a plurality of encapsulated air bubbles. In one illustrative example, the bubble in a marker **208** can be formed by introducing air by a syringe (not shown) penetrating the wall of the sheath **246** and thereafter sealing the hole created by the syringe with epoxy.

Optionally, a plurality of markers **208** can be disposed in the front distal section **259**. The markers **208** can be sized and configured to aid in locating and identifying the orientation of the distal end section **259**. For example, the markers **208** can

be located and/or viewed with external ultrasonic imaging systems (not shown), such as those commonly used in similar medical procedures.

A further advantage is provided where the stent delivery applicator **201** is both steerable and configured for multiple stent implantation. As such, the applicator **201** can be inserted into the anterior chamber **20**, through an incision, such as a corneal incision, and multiple stents can then be implanted at different locations without removing the applicator **201** or creating other incisions, described in greater detail below.

FIG. **52**A shows another embodiment of the stent delivery distal portion **241**, identified generally by the reference numeral **241**B, and another embodiment of a stent, identified generally by the reference numeral **229**E.

The stent **229**E comprises a first (proximal) flange **240**E and a second (distal) flange **237**E with a plurality of supporting legs or posts **236**. The second flange **237**E of the stent **229**E is configured to be foldable. For example, the first flange **237**E can be configured to be elastically foldable toward an upstream direction. As such, the first flange **237**E can be folded toward an upstream direction, as illustrated in FIG. **52**A when stored in the sheath **246**. Thus, after the first flange **237**E has been pushed through the end **242**, the first flange **237**E can resiliently unfold. As such, the first flange **237**E can provide enhanced anchoring for the stent **229**E when implanted into the trabecular meshwork **21**.

A further advantage can be provided where the applicator **201** includes a cutting device that can extend through the lumens **239**E of the stents **229**E. For example, as shown in FIG. **52**A, a cutting device **250** can include a cutting tip **247** and can be configured to extend through the stents **229**E during an implantation procedure. As such, the cutting device can being an incision at the center of the site at which the stent **229**E is to be inserted through the trabecular meshwork **21**. In the illustrated embodiment, the cutting device is in the form of a trocar.

With continued reference to FIG. **52**A, the cutting device **250** is configured to be moveable axially through the lumen **249** of the applicator end portion **241**B of the sheath **146**. Additionally, the cutting device **250** can be moved axially relative to the stent or stents through which it extends.

Another advantage can be provided where the cutting device **250** also includes at least one holding member for holding a stent. For example, the cutting device **250** includes at least one holding device **245**, described above with reference to FIG. **51**B, can be configured to hold a stent at least during an implantation procedure, and to release the stent at the appropriate time.

Preferably, the holding members **245**B are arranged to align the sides of the cutting tip **247** with the distally facing sides of the flange **237**E when the flange **237**E is folded. For example, as shown in FIG. **52**A, when the flange **237**E is folded, the distally facing side of the flange **237**E is aligned with the sides of the cutting tip **247**, as indicated by the dashed-lines identified by the letter "A." This alignment can be facilitated by arranging the holding members **245**B such that the cutting device **250** extends distally from the flange **237**E sufficiently to cause the sides of the cutting tip **247** to become aligned with the flange **237**E. As such, the sides of the cutting tip **247** and the distally facing side of the flange **237**E generate a more smooth surface for penetrating the trabecular meshwork **21** during an implantation procedure.

During operation, the applicator end portion **241**B can be pushed into trabecular meshwork **21**, with the flange **237**E disposed in Schlemm's canal **22**, as shown in FIG. **52**B. The sheath **246** can then be retracted out of Schlemm's canal **22**, leaving the cutting device **250** and stent **229**E in place (FIG. **52**C).

With the sheath **246** retracted, the first flange **237**E can unfold, as indicated by the arrows U in FIG. **52**C, thereby providing enhanced anchoring of the stent **229**E within Schlemm's canal **22** (FIG. **52**D). Additionally, the second flange **240**E is within the anterior chamber **20**.

As shown in FIG. **52**D, the cutting device **250** can then be retracted relative to the applicator end portion **241**B and the stent **229**E, leaving the stent **229**E in place. Optionally, the cutting device **250** and the sheath **246** can be retracted together.

As noted above, the holding members **245** are configured to limit the movement of the stents **229**E relative to the cutting device **250**. When the cutting device is retracted, the next stent **229**E preferably is moved passed (in the downstream direction) the holding member **245** that was previously between the stents **229**E. As such, the next stent **229**E can be moved into position for implantation. Thus, the holding members **245** preferably are configured to allow the stent **229**E to move toward the cutting tip **247** when the cutting device **250** is retracted. For example, the holding members **245** can be controlled so as to retract when the cutting device **250** is retracted.

With reference to FIG. **53**, another embodiment of an axisymmetric trabecular stenting device is illustrated therein and identified generally by the reference numeral **229**F. For ease of description, but without limitation, the stent **229**F is described below with reference to cylindrical coordinates of x, r and angle α as shown in FIG. **53**.

The stent **229**F comprises an inlet (proximal) section having a first flange **240**F, an outlet (distal) section having a second flange **237**F and a middle section **284** connecting the inlet section and the outlet section. A lumen **239**F of the device **229**F is configured to transport aqueous, liquid, or therapeutic agents between the inlet section and the outlet section. As referred to herein, "therapeutic agent" is intended to include pharmaceutical agents, drugs, genes, cells, proteins, and/or growth factors.

The inlet section of the stent **229**F has at least one inlet opening **286** and the outlet section comprises at least one outlet opening **287**. A further advantage is provided where the outlet section **237**F includes at least one opening **287**, **288** suitably located for discharging substantially axisymmetrically the aqueous, liquid or therapeutic agents, wherein the opening **287**, **288** is in fluid communication with the lumen **285** of the device **281**. In the illustrated embodiment, the openings **288** extend radially from the lumen **285** and open at the outwardly facing surface around the periphery of the outlet flange **237**F.

In one embodiment of an implantation procedure, Pilocarpine is administered preoperatively to constrict the pupil to provide maximal protection of the lens in phakic individuals and to further open the anterior chamber angle to provide a better view of the surgical site. Topical and retrobulbar anesthetic are recommended. A small self-sealing temporal corneal incision can be made and Healon® viscoelastic (VE) can be injected to maintain the anterior chamber.

A microscope can be tilted slightly toward the surgeon and the patient's head can be rotated away from the surgeon to provide a suitable view of the nasal trabecular meshwork using a direct-view gonioscope that is placed on the eye. The applicator **201** with a preloaded stent, such as, for example, but without limitation, an one or any combination of the stents a plurality of any combination of the stents **229**, **30**, **30***a*, **30***b*, **30***c*, **30***d*, **30***e*, **30***f*, **30***g*, **30***h*, **30***i*, **30***j*, **30***k*, **30***m*, **30***n*, **30***p*, **30***q*,

30*r*, 30*s*, 30*t*, 30*u*, 30*v*, 229A, 229B, 229C, 229D, 229E, 229F, or any of the other stents described below, is advanced through the corneal wound and across the anterior chamber. The stent is pushed against the trabecular meshwork and moved inferiorly to pierce the trabecular meshwork and guide the stent into Schlemm's canal. After successful implantation and release of the stent, the applicator is withdrawn and the VE is flushed from the eye.

The G2 stent (for example, stent 229F of FIG. 53) can be smaller and of a significantly different design than the G1 stents, thus allowing it to be passed through a smaller corneal incision and be implanted with a simple axial motion. Reduced size and simplified surgical motions may enable implantation of the G2 stent without the use of viscoelastic and therefore eliminate a significant expendable material cost and the time necessary to administer and remove it.

Additionally, viscoelastic use in patients undergoing eye surgery can cause post-operative transient IOP spikes that can further damage the remaining glaucoma-compromised retina. Reduced surgical manipulations reduce the burden on the surgeon and reduce the stimulation and irritation of intraocular tissues. Furthermore, reduction in the corneal incision size raises the possibility that the incision could be made by the G2 applicator, and could potentially reduce the surgical implant procedure to an injectable implant procedure. Injectable stent therapy represents a potentially superior alternative to both end-stage surgical therapy and to patients burdened by the cumulative side effects, complications, and compliance issues associated with drug therapy.

The G2 stent and applicator system are sized, dimensioned and configured for placement through trabecular meshwork in an ab interno or ab externo procedures. FIGS. 54A-C illustrate additional examples of preferred G2 stent and applicator embodiments.

FIG. 54A shows yet another embodiment of a stent injector assembly for multiple stent deployment, identified generally by the reference numeral 260. The stent injector 260 comprises a housing 261 with a distal cap 262 and a distal stent-holding element 263 that is distal from the distal cap 261. Optionally, at least a portion of the distal stent-holding element 263 can be configured to be steerable with a steering mechanism that can be constructed in accordance with the description of the steerable section 251 described above with reference to FIGS. 51A-D.

The stent-holding element 263 can comprise an elongate member 264 with at least one stent slideably disposed thereon. The elongate member 264 can be configured to extend through the lumen of any of the stents 229A, 229B, 229C, 229D, 229E, 229F, or any of the other stents described below.

In the illustrated embodiment, the elongate member 264 extends through the lumen of stents 229G (FIG. 54B). In one embodiment, the distal stent 229G can be the same as the second or proximal stent 229G. In another embodiment, the distal stent and the proximal stent are different in size or configuration for placement at different locations. For example, the proximal and distal stents of FIG. 54B can be any combination of the stents 229A, 229B, 229C, 229D, 229E, 229F, and 229G. Additionally, the applicator 260 can be configured to be loaded with only one, three, or more stents.

In the illustrated embodiment, the distal flange 237G of the stent 229G can be wedge-shaped. For example, the distal end of the flange 237G can have a smaller diameter than that of the proximal end of the flange 237G. As such, the stent 229G can pass more easily through the trabecular meshwork 21. Additionally, the distally facing surface of the flange 237G can be inclined so as to be aligned with a distal surface of the elongate member 264. As noted above with respect to the cutting member 250, the elongate member 264 can be in the form of a trocar.

The stent-holding element further comprises a sleeve 265 configured to support the elongate member 264. The sleeve 265 (for example, made of hypo tubing) can be pressed or bonded onto the distal cap 262 to form a sleeve-cap subassembly. The elongate member 264 can be configured to be axially moveable relative to the sleeve 265, as indicated by the arrow 266 (FIG. 54C).

The housing 261 can also comprise a tip actuator 267 that has a distal end 268 and a proximal end 269. The elongate member 264 can be press fit or bonded into the distal end portion of the tip actuator 267 to form a tip/tip actuator subassembly. In one exemplary but non-limiting embodiment, the elongate member 264 can be a 0.08 mm diameter sharpened rod made from a hard material, such as a metal.

The tip/tip actuator subassembly is fed through the sleeve-cap subassembly and the cap 262 is screwed onto or bonded with the housing 261. The proximal end 269 can include a threaded portion 270 adapted for threaded engagement with a rotation knob 271 located at the proximal end portion of the housing 261. Thus, the coupling mechanism comprises the tip/tip-actuator subassembly screwed into the rotation knob 271 to form an actuator-knob subassembly.

An interlock arrangement 272 is configured to retain the knob 271 on the housing 261 and allow the knob 271 to rotate relative to the housing 261. The interlock arrangement 272 can include an annular rib disposed on the housing 261 and a groove disposed on the knob 271. A clearance is provided between the groove and the rib so as to allow the knob 271 to rotate freely relative to the housing 261. The knob 271 can be pressed onto the housing 261 and thus spins freely on housing 261 without coming off because of an interlock arrangement 272.

With reference to FIGS. 54A and 54C, the housing 261 can include a slot line 273 at a location perpendicular to a longitudinal axis 275 of the housing. One side of the slot line 273 can be drilled through to the opposite side of the housing, thus allowing an anti-rotation pin 274 to extend therethrough.

FIG. 54C shows a top cross-sectional view, identified as section 3-3 of FIG. 54A, with the anti-rotation pin 274 aligned with the slot 276. During assembly, of the injector 260, the tip actuator 267 is rotated until the slot 276 is aligned with the drilled hole adapted for the anti-rotation pin 274 to extend into the drilled hole. The anti-rotation pin 274 is pressed through a first side of housing, through the tip actuator, and through a second opposite side of housing.

In operation, one or more stents are placed over the member 264 and against the blunt front end of the sleeve 265. After the injector approaches the target site, the elongate member 264 and the first stent are pressed into tissue where implantation is to take place. In an ab interno procedure, the first tissue is the trabecular meshwork facing the anterior chamber. In an ab externo procedure, the first tissue is the trabecular meshwork facing Schlemm's canal. Once the first stent is in a proper location, the knob 271 is rotated to withdraw the elongate member 264, leaving the first stent in place. Stents can be snugly held onto the tip 264 with a mechanical feature on the elongate member, such as the holding members 245 described above with reference to FIGS. 51A-D. Optionally, the sleeve 265 can include a mechanical feature for holding stents in place. Further viscoelastic material or other means can be provided for holding the stents so that stent deployment does not occur until desired.

FIG. **55** shows an embodiment of the seton implant **331** constructed according to the principles of the invention. The seton implant may comprise a biocompatible material, such as a medical grade silicone, for example, the material sold under the trademark Silastic™, which is available from Dow Corning Corporation of Midland, Mich., or polyurethane, which is sold under the trademark Pellethane™, which is also available from Dow Corning Corporation. In an alternate embodiment, other biocompatible materials (biomaterials) may be used, such as polyvinyl alcohol, polyvinyl pyrrolidone, collagen, heparinized collagen, tetrafluoroethylene, fluorinated polymer, fluorinated elastomer, flexible fused silica, polyolefin, polyester, polysilicon, mixture of biocompatible materials, and the like. In a further alternate embodiment, a composite biocompatible material by surface coating the above-mentioned biomaterial may be used, wherein the coating material may be selected from the group consisting of polytetrafluoroethylene (PTFE), polyimide, hydrogel, heparin, therapeutic drugs, and the like.

The main purpose of the seton implant is to assist in facilitating the outflow of aqueous in an outward direction **340** into the Schlemm's canal and subsequently into the aqueous collectors and the aqueous veins so that the intraocular pressure is balanced. In one embodiment, the seton implant **331** comprises an elongated tubular element having a distal section **332** and an inlet section **344**. A rigid or flexible distal section **332** is positioned inside one of the existing outflow pathways. The distal section may have either a tapered outlet end **333** or have at least one ridge **337** or other retention device protruding radially outwardly for stabilizing the seton implant inside the existing outflow pathways after implantation. For stabilization purposes, the outer surface of the distal section **332** may comprise a stubbed surface, a ribbed surface, a surface with pillars, a textured surface, or the like. The outer surface **336**, including the outer region **335** and inner region **334** at the outlet end **333**, of the seton implant is biocompatible and tissue compatible so that the interaction/irritation between the outer surface and the surrounding tissue is minimized. The seton implant may comprise at least one opening at a location proximal the distal section **332**, away from the outlet end **333**, to allow flow of aqueous in more than one direction. The at least one opening may be located on the distal section **332** at about opposite of the outlet end **333**.

In another exemplary embodiment, the seton implant **331** may have a one-way flow controlling means **339** for allowing one-way aqueous flow **340**. The one-way flow controlling means **339** may be selected from the group consisting of a check valve, a slit valve, a micropump, a semi-permeable membrane, or the like. To enhance the outflow efficiency, at least one optional opening **341** in the proximal portion of the distal section **332**, at a location away from the outlet end **333**, and in an exemplary embodiment at the opposite end of the outlet end **333**, is provided.

FIG. **56** shows a top cross-sectional view of FIG. **55**. The shape of the opening of the outlet end **333** and the remaining body of the distal section **332** may be oval, round or some other shape adapted to conform to the shape of the existing outflow pathways. This configuration will match the contour of Schlemm's canal to stabilize the inlet section with respect to the iris and cornea by preventing rotation.

As shown in FIG. **55**, the seton implant of the present invention may have a length between about 0.5 mm to over a meter, depending on the body cavity the seton implant applies to. The outside diameter of the seton implant may range from about 30 μm to about 500 μm. The lumen diameter is preferably in the range between about 20 μm to about 150 μm. The seton implant may have a plurality of lumens to facilitate multiple flow transportation. The distal section may be curved at an angle between about 30 degrees to about 150 degrees, in an exemplary embodiment at around 70-110 degrees, with reference to the inlet section **344**.

FIG. **57** shows another embodiment of the seton implant **345** constructed in accordance with the principles of the invention. In an exemplary embodiment, the seton implant **345** may comprise at least two sections: an inlet section **347** and an outlet section **346**. The outlet section has an outlet opening **48** that is at the outlet end of the seton implant **345**. The shape of the outlet opening **348** is preferably an oval shape to conform to the contour of the existing outflow pathways. A portion of the inlet section **347** adjacent the joint region to the outlet section **346** will be positioned essentially through the diseased trabecular meshwork while the remainder of the inlet section **347** and the outlet section **346** are outside the trabecular meshwork. As shown in FIG. **5**, the long axis of the oval shape opening **348** lies in a first plane formed by an X-axis and a Y-axis. To better conform to the anatomical contour of the anterior chamber **20**, the trabecular meshwork **21** and the existing outflow pathways, the inlet section **347** may preferably lie at an elevated second plane, at an angle θ, from the first plane formed by an imaginary inlet section **347**A and the outlet section **346**. The angle θ may be between about 30 degrees and about 150 degrees.

After the first stent is implanted, the injector is slightly withdrawn away from the trabecular meshwork. The tip of the injector is moved and pointed to a second target site without withdrawing the injector from the incision on the sclera. This re-positioning of the injector can be accomplished with a steerable section of the injector **260** noted above.

The term "targeted placement" of trabecular stents refers to the intentional placement of a stent at a particular location in Schlemm's canal for the purpose of providing a maximum benefit in the form of maximum outflow facility. With reference to FIG. **50**A, aqueous enters Schlemm's canal **22** through the trabecular meshwork **21** and travels along the canal to exit through the collector channels **23**. Schlemm's canal is a narrow channel with approximate dimensions of 250 μm×20 μm with a 40 mm length (Volume~0.2 μl) and it provides measurable resistance to the flow of aqueous. Therefore, placing a stent into Schlemm's canal **22** through the trabecular meshwork **21** yields the best improvement in outflow facility when it is placed near a large collector channel **23** or a group of smaller ones that combine to have a larger hydraulic diameter. It is one aspect of the present invention to locate/detect the most appropriate collector channel(s) to implant a trabecular shunting stent adjacent the collector channel(s) **23**.

The term "Multi-stent therapy" refers to the intentional placement of a stent in each of several locations in Schlemm's canal **22**. Since Schlemm's canal **22** has measurable resistance to flow at physiological flow rates, a plurality of stents is strategically placed close to concentrations of collector ducts **23** or a large collector and distributed around Schlemm's canal **22** to maximize the impact of multiple stents.

An injector or device applicator to hold a plurality of serial devices has advantages of placing the device one at a time without reloading the device or without completely withdrawing the applicator out of a portion of the body. The advantages may include saving operating time, reducing redundant incision or injury, or exact positioning for device placement.

By way of example, but without limitation, an injector or device applicator for multiple device deployment may be used for implanting punctum plugs in an eye, for implanting

drug-eluting devices into sclera tissue of an eye, implanting drug-eluting devices into tissue of a posterior segment, or implanting cardiovascular stents. Some aspects of at least one of the inventions disclosed herein relate to a method of multiple device deployment comprising: (a) loading a plurality of devices within a device-retaining space of a device applicator; (b) delivering the applicator to a first target implant site; (c) deploying a first device at the first target implant site; (d) detaching the applicator from the first target implant site; (e) directing the applicator to a second target implant site; (f) deploying a second device at the second target implant site; and (g) withdrawing the applicator.

The device of the exemplary embodiment preferably comprises a biocompatible material such that inflammation arising due to irritation between the outer surface of the device and the surrounding tissue is minimized. Biocompatible materials which may be used for the device **81** preferably include, but are not limited to, titanium, titanium alloys, polypropylene, nylon, PMMA (polymethyl methacrylate), medical grade silicone, e.g., Silastic™, available from Dow Corning Corporation of Midland, Mich.; and polyurethane, e.g., Pellethane™, also available from Dow Corning Corporation.

In other embodiments, the device of the embodiments may comprise other types of biocompatible material, such as, by way of example, polyvinyl alcohol, polyvinyl pyrrolidone, collagen, heparinized collagen, polytetrafluoroethylene, expanded polytetrafluoroethylene, fluorinated polymer, fluorinated elastomer, flexible fused silica, polyolefin, polyester, polysilicon, and/or a mixture of the aforementioned biocompatible materials, and the like. In still other embodiments, composite biocompatible material may be used, wherein a surface material may be used in addition to one or more of the aforementioned materials. For example, such a surface material may include polytetrafluoroethylene (PTFE) (such as Teflon™), polyimide, hydrogel, heparin, therapeutic drugs (such as beta-adrenergic antagonists and other anti-glaucoma drugs, or antibiotics), and the like.

FIG. **58** illustrates a preferred embodiment of a trabecular shunting/stenting device **431**, which facilitates the outflow of aqueous from the anterior chamber **20** into Schlemm's canal **22**, and subsequently into the aqueous collectors and the aqueous veins so that intraocular pressure is reduced. In the illustrated embodiment, the trabecular stenting device **431** comprises an inlet section **402**, having an inlet opening **403**, a middle section **404**, and an outlet section **409**. The middle section **404** may be an extension of, or may be coextensive with, the inlet section **402**. The outlet section **409** is preferably somewhat flexible to facilitate positioning of the outlet section **409** within an outflow pathway of the eye **10**. The outlet section **409** is preferably substantially perpendicular to the middle section **404**. "Substantially perpendicular," as used herein, is defined as subtending an angle between longitudinal axes of the sections **404**, **409** ranging between about 30 degrees and about 150 degrees. The device **431** further comprises at least one lumen **407** within sections **404** and **409** which is in fluid communication with the inlet opening **403** of section **402**, thereby facilitating transfer of aqueous through the device **431**.

In one embodiment, the outlet section **409** has at least one outlet end. In another embodiment, the outlet section preferably has a first outlet end **406** and a second, opposite outlet end **405**. The lumen **407** within the outlet section **409** opens to at least one of the outlet ends **405**, **406**. Furthermore, the outlet section **409** may have a plurality of side openings **477**, each of which is in fluid communication with the lumen **407**, for transmission of aqueous. The middle section **404** is connected to or coextensive with the outlet section **409** and is disposed between the first outlet end **406** and the second outlet end **405**. In a preferred embodiment, the outlet section **409** is curved around a point, or a curve center, and the middle section **404** extends substantially along a plane that contains the curve center. In this embodiment, the outlet section **409** has a radius of curvature ranging between about 4 mm and about 10 mm.

As will be apparent to a person skilled in the art, the lumen **407** and the remaining body of the outlet section **409** may have a cross-sectional shape that is oval, circular, or other appropriate shape. The cross-sectional shapes of the lumen **407** and the outlet section **409** preferably conform to the shape of the outflow pathway into which the outlet section **409** is placed. The opening of the lumen **407** of the outlet ends **405**, **406** may be ovoid in shape to match the contour of Schlemm's canal **22**. Further, an outer contour of the outlet section **409** may be elliptical (e.g., ovoid) in shape to match the contour of Schlemm's canal **22**. This serves to minimize rotational movement of the outlet section **409** within Schlemm's canal **22**, and thereby stabilizes the inlet section **402** with respect to the iris and cornea.

A circumferential ridge **408** is provided at the junction of the inlet section **402** and the middle section **404** to facilitate stabilization of the device **431** once implanted within the eye **10**. Preferably, the middle section **404** has a length (between the ridge **408** and the outlet section **409**) that is roughly equal to a thickness of the trabecular meshwork **21**, which typically ranges between about 100 μm and about 300 μm. In addition, the outlet section **409** may advantageously be formed with a protuberance or spur projecting therefrom so as to further stabilize the device **431** within the eye **10** without undue suturing.

FIG. **63** is a close-up view of the inlet section **402** of the trabecular stenting device **431**, illustrating a flow-restricting member **472**, which is tightly retained within a lumen **478**. The flow-restricting member **472** is shown located close to an inlet side **471** of the inlet section **402**. The flow-restricting member **472** serves to selectively restrict at least one component in blood from moving retrograde, i.e., from the outlet section **409** into the anterior chamber **20** of the eye **10**. Alternatively, the flow-restricting member **472** may be situated in any location within the device **431** such that blood flow is restricted from retrograde motion. The flow-restricting member **472** may, in other embodiments, be a filter made of a material selected from the following filter materials: expanded polytetrafluoroethylene, cellulose, ceramic, glass, Nylon, plastic, and fluorinated material such as polyvinylidene fluoride ("PVDF") (trade name: Kynar, by DuPont).

The trabecular stenting device **431** may be made by molding, thermo-forming, or other micro-machining techniques. The trabecular stenting device **431** preferably comprises a biocompatible material such that inflammation arising due to irritation between the outer surface of the device **431** and the surrounding tissue is minimized. Biocompatible materials which may be used for the device **431** preferably include, but are not limited to, titanium, medical grade silicone, e.g., Silastic™, available from Dow Corning Corporation of Midland, Mich.; and polyurethane, e.g., Pellethane™, also available from Dow Corning Corporation. In other embodiments, the device **431** may comprise other types of biocompatible material, such as, by way of example, polyvinyl alcohol, polyvinyl pyrrolidone, collagen, heparinized collagen, polytetrafluoroethylene, expanded polytetrafluoroethylene, fluorinated polymer, fluorinated elastomer, flexible fused silica, polyolefin, polyester, polysilicon, and/or a mixture of the aforementioned biocompatible materials, and the like. In still

other embodiments, composite biocompatible material may be used, wherein a surface material may be used in addition to one or more of the aforementioned materials. For example, such a surface material may include polytetrafluoroethylene (PTFE) (such as Teflon™), polyimide, hydrogel, heparin, therapeutic drugs (such as beta-adrenergic antagonists and other anti-glaucoma drugs, or antibiotics), and the like.

As is well known in the art, a device coated or loaded with a slow-release substance can have prolonged effects on local tissue surrounding the device. The slow-release delivery can be designed such that an effective amount of substance is released over a desired duration. "Substance," as used herein, is defined as any therapeutic or bioactive drug or agents that can stop, mitigate, slow-down or reverse undesired disease processes.

In one embodiment, the device **431** may be made of a biodegradable (also including bioerodible) material admixed with a substance for substance slow-release into ocular tissues. In another embodiment, polymer films may function as substance containing release devices whereby the polymer films may be coupled or secured to the device **431**. The polymer films may be designed to permit the controlled release of the substance at a chosen rate and for a selected duration, which may also be episodic or periodic. Such polymer films may be synthesized such that the substance is bound to the surface or resides within a pore in the film so that the substance is relatively protected from enzymatic attack. The polymer films may also be modified to alter their hydrophilicity, hydrophobicity and vulnerability to platelet adhesion and enzymatic attack. In one embodiment, the polymer film is made of biodegradable material.

Furthermore, the film may be coupled (locally or remotely) to a power source such that when substance delivery is desired, a brief pulse of current is provided to alter the potential on the film to cause the release of a particular amount of the substance for a chosen duration. Application of current causes release of a substance from the surface of the film or from an interior location in the film such as within a pore. The rate of substance delivery is altered depending on the degree of substance loading on the film, the voltage applied to the film, and by modifying the chemical synthesis of substance delivery polymer film.

The power-activated substance delivery polymer film may be designed to be activated by an electromagnetic field, such as, by way of example, NMR, MRI, or short range RF transmission (such as a Bluetooth® apparatus). In addition, ultrasound can be used to cause a release of a particular amount of substance for a chosen duration. This is particularly applicable to a substance coated device or a device made of a substrate containing the desired substance.

The device **431** may be used for a direct release of pharmaceutical preparations into ocular tissues. As discussed above, the pharmaceuticals may be compounded within the device **431** or form a coating on the device **431**. Any known drug therapy for glaucoma may be utilized, including but not limited to, the following:

U.S. Pat. No. 6,274,138, issued Aug. 14, 2001, and U.S. Pat. No. 6,231,853, issued May 15, 2001, the entire contents of both of which are incorporated herein by reference, disclose the function of mitochondria and toxic substances synthesized as a metabolic byproduct within mitochondria of cells. Perry and associates (Perry H D et al. "Topical cyclosporin A in the management of postkeratoplasty glaucoma" *Cornea* 16:284-288, 1997) report that topical cyclosporin-A has been shown to reduce post-surgical increases in intraocular pressure. It is proposed that such compounds with known effects on mitochondrial stability might be effective in treating trabecular meshwork. An antagonistic drug to neutralize the toxic byproduct or a stabilizing drug to effect mitochondrial stability is believed able to restore the mitochondria function and subsequently mitigate the dysfunction of the trabecular meshwork.

U.S. Pat. No. 6,201,001, issued Mar. 13, 2001, the entire contents of which are incorporated herein by reference, discloses Imidazole antiproliferative agents useful for neovascular glaucoma.

U.S. Pat. No. 6,228,873, issued May 8, 2001, the entire contents of which are incorporated herein by reference, discloses a new class of compounds that inhibit function of sodium chloride transport in the thick ascending limb of the loop of Henle, wherein the preferred compounds useful are furosemide, piretanide, benzmetanide, bumetanide, torasernide and derivatives thereof.

U.S. Pat. No. 6,194,415, issued Feb. 27, 2001, the entire contents of which are incorporated herein by reference, discloses a method of using quinoxalines (2-imidazolin-2-ylamino) in treating neural injuries (e.g., glaucomatous nerve damage).

U.S. Pat. No. 6,060,463, issued May 9, 2000, and U.S. Pat. No. 5,869,468, issued Feb. 9, 1999, the entire contents of which are incorporated herein by reference, disclose treatment of conditions of abnormally increased intraocular pressure by administration of phosphonylmethoxyalkyl nucleotide analogs and related nucleotide analogs.

U.S. Pat. No. 5,925,342, issued Jul. 20, 1999, the entire contents of which are incorporated herein by reference, discloses a method for reducing intraocular pressure by administration of potassium channel blockers.

U.S. Pat. No. 5,814,620, issued Sep. 29, 1998, the entire contents of which are incorporated herein by reference, discloses a method of reducing neovascularization and of treating various disorders associated with neovascularization. These methods include administering to a tissue or subject a synthetic oligonucleotide.

U.S. Pat. No. 5,767,079, issued Jun. 16, 1998, the entire contents of which are incorporated herein by reference, discloses a method for treatment of ophthalmic disorders by applying an effective amount of Transforming Growth Factor-Beta (TGF-beta) to the affected region.

U.S. Pat. No. 5,663,205, issued Sep. 2, 1997, the entire contents of which are incorporated herein by reference, discloses a pharmaceutical composition for use in glaucoma treatment which contains an active ingredient 5-[1-hydroxy-2-[2-(2-methoxyphenoxyl)ethylamino]ethyl]-2-methylbenzenesulfonamide. This agent is free from side effects, and stable and has an excellent intraocular pressure reducing activity at its low concentrations, thus being useful as a pharmaceutical composition for use in glaucoma treatment.

U.S. Pat. No. 5,652,236, issued Jul. 29, 1997, the entire contents of which are incorporated herein by reference, discloses pharmaceutical compositions and a method for treating glaucoma and/or ocular hypertension in the mammalian eye by administering thereto a pharmaceutical composition which contains as the active ingredient one or more compounds having guanylate cyclase inhibition activity. Examples of guanylate cyclase inhibitors utilized in the pharmaceutical composition and method of treatment are methylene blue, butylated hydroxyanisole and N-methylhydroxylamine.

U.S. Pat. No. 5,547,993, issued Aug. 20, 1996, the entire contents of which are incorporated herein by reference, discloses that 2-(4-methylaminobutoxy) diphenylmethane or a hydrate or pharmaceutically acceptable salt thereof have been found useful for treating glaucoma.

U.S. Pat. No. 5,502,052, issued Mar. 26, 1996, the entire contents of which are incorporated herein by reference, discloses use of a combination of apraclonidine and timolol to control intraocular pressure. The compositions contain a combination of an alpha-2 agonist (e.g., para-amino clonidine) and a beta blocker (e.g., betaxolol).

U.S. Pat. No. 6,184,250, issued Feb. 6, 2001, the entire contents of which are incorporated herein by reference, discloses use of cloprostenol and fluprostenol analogues to treat glaucoma and ocular hypertension. The method comprises topically administering to an affected eye a composition comprising a therapeutically effective amount of a combination of a first compound selected from the group consisting of beta-blockers, carbonic anhydrase inhibitors, adrenergic agonists, and cholinergic agonists, together with a second compound.

U.S. Pat. No. 6,159,458, issued Dec. 12, 2000, the entire contents of which are incorporated herein by reference, discloses an ophthalmic composition that provides sustained release of a water soluble medicament formed by comprising a crosslinked carboxy-containing polymer, a medicament, a sugar and water.

U.S. Pat. No. 6,110,912, issued Aug. 29, 2000, the entire contents of which are incorporated herein by reference, discloses methods for the treatment of glaucoma by administering an ophthalmic preparation comprising an effective amount of a non-corneotoxic serine-threonine kinase inhibitor, thereby enhancing aqueous outflow in the eye and treatment of the glaucoma. In some embodiments, the method of administration is topical, whereas it is intracameral in other embodiments. In still further embodiments, the method of administration is intracanalicular.

U.S. Pat. No. 6,177,427, issued Jan. 23, 2001, the entire contents of which are incorporated herein by reference, discloses compositions of non-steroidal glucocorticoid antagonists for treating glaucoma or ocular hypertension.

U.S. Pat. No. 5,952,378, issued Sep. 14, 1999, the entire contents of which are incorporated herein by reference, discloses the use of prostaglandins for enhancing the delivery of drugs through the uveoscleral route to the optic nerve head for treatment of glaucoma or other diseases of the optic nerve as well as surrounding tissue. The method for enhancing the delivery to the optic nerve head comprises contacting a therapeutically effective amount of a composition containing one or more prostaglandins and one or more drug substances with the eye at certain intervals.

FIG. **59** illustrates another embodiment of a trabecular stenting device **431**A that facilitates the outflow of aqueous from the anterior chamber **20** into Schlemm's canal **22**, and subsequently into the aqueous collectors and the aqueous veins so that intraocular pressure is reduced. The device **431**A comprises an inlet section **402**A, a middle section **404**A, and an outlet section **409**A. The device **431**A further comprises at least one lumen **403**A traversing the sections **402**A, **404**A, **409**A and providing fluid communication therebetween. The lumen **403**A facilitates the transfer of aqueous from the inlet section **402**A through the device **431**A. The outlet section **409**A is preferably curved, and may also be somewhat flexible, to facilitate positioning of the outlet section **409**A within an existing outflow pathway of the eye **10**. The outlet section **409**A may further comprise an elongate trough **7**A for transmitting, or venting, aqueous. The elongate trough **7**A is connected to and in fluid communication with the lumen **403**A within the trabecular stenting device **431**A.

A circumferential ridge **8**A is provided at the junction of the inlet section **402**A and the middle section **404**A to facilitate stabilization of the device **431**A once implanted within the eye **10**. Preferably, the middle section **404**A has a length (between the ridge **8**A and the outlet section **409**A) that is roughly equal to the thickness of the trabecular meshwork **21**, which typically ranges between about 100 μm and about 300 μm. In addition, the outlet section **409**A may advantageously be formed with a protuberance or barb projecting therefrom so as to further stabilize the device **431**A within the eye **10** without undue suturing.

As will be appreciated by those of ordinary skill in the art, the devices **431** and **431**A may advantageously be practiced with a variety of sizes and shapes without departing from the scope of the invention. Depending upon the distance between the anterior chamber **20** and the drainage vessel (e.g., a vein) contemplated, the devices **431**, **431**A may have a length ranging from about 0.05 centimeters to over 10 centimeters. Preferably, the devices **431** and **431**A have an outside diameter ranging between about 30 μm and about 500 μm, with the lumens **407**, **403**A having diameters ranging between about 20 μm and about 250 μm, respectively. In addition, the devices **431**, **431**A may have a plurality of lumens to facilitate transmission of multiple flows of aqueous. The inlet sections **402**, **402**A have longitudinal axes that form an angle (θ) ranging between about 20 degrees and about 150 degrees relative to the longitudinal axes of the middle sections **404**, **404**A, respectively. More preferably, the angles between the longitudinal axes of the inlet sections **402**, **402**A and the middle sections **404**, **404**A range between about 30 degrees and about 60 degrees, respectively.

One preferred method for increasing aqueous outflow in the eye **10** of a patient, to reduce intraocular pressure therein, comprises bypassing the trabecular meshwork **21**. In operation, the middle section **404** of the device **431** is advantageously placed across the trabecular meshwork **21** through a slit or opening. This opening can be created by use of a laser, a knife, or other surgical cutting instrument. The opening may advantageously be substantially horizontal, i.e., extending longitudinally in the same direction as the circumference of the limbus **15**. Other opening directions may also be used, as well. The opening may advantageously be oriented at any angle, relative to the circumference of the limbus **15**, that is appropriate for inserting the device **431** through the trabecular meshwork **21** and into Schlemm's canal **22** or other outflow pathway, as will be apparent to those skilled in the art. The middle section **404** may be semi-flexible and/or adjustable in position relative to the inlet section **402** and/or the outlet section **409**, further adapting the device **431** for simple and safe glaucoma implantation. Furthermore, the outlet section **409** may be positioned into fluid collection channels of the natural outflow pathways. Such natural outflow pathways include Schlemm's canal **22**, aqueous collector channels, aqueous veins, and episcleral veins. The outlet section **409** may be positioned into fluid collection channels up to at least the level of the aqueous veins, with the device inserted in a retrograde or antegrade fashion.

FIG. **60** generally illustrates a step in the implantation of the trabecular stenting device **431** through the trabecular meshwork **21**. The outlet section **409** of the device **431** is inserted into an opening **61** in the trabecular meshwork **21**. A practitioner may create the opening **61** "ab interno" from the interior surface **65** of the trabecular meshwork **21**. The practitioner then advances the first outlet end **406** of the outlet section **409** through the opening **61** into a first side of Schlemm's canal **22** or other suitable outflow pathway within the eye **10**. Next, the practitioner advances the second outlet end **405** through the opening **61** and into a second side of Schlemm's canal **22**. The advancing of the second outlet end **405** may be facilitated by slightly pushing the second outlet end **405** through the opening **61**.

FIG. **62** generally illustrates a further stage in deployment of the device **31**, wherein the entire outlet section **409** of the device **431** is implanted within Schlemm's canal **22**, beneath the trabecular meshwork **21**. At this stage, the lumen **403** of the implanted device **431** provides an enhanced fluid communication through the trabecular meshwork **21**.

FIG. **61** shows an additional and/or alternate step in the implantation of the trabecular stenting device **431** through the trabecular meshwork **21**. The practitioner inserts a distal end **463** of a guidewire **464** through the opening **61** into the first side of Schlemm's canal **22**. The practitioner then advances the first outlet end **406** of the outlet section **409** into Schlemm's canal **22** by "riding," or advancing, the trabecular stenting device **431** on the guidewire **464**. As will be apparent to those skilled in the art, the guidewire **464** will have a shape and size conforming to the shape and size of the lumen **7**; and as such, may have an elliptical (e.g., oval) shape, a D-shape, a round shape, or an irregular (asymmetric) shape which is adapted for nonrotatory engagement for the device **31**.

Another method for increasing aqueous outflow within the eye **10** of a patient, and thus reduce intraocular pressure therein, comprises: (a) creating an opening in the trabecular meshwork **21**, wherein the trabecular meshwork **21** includes a deep side and superficial side; (b) inserting the trabecular stenting device **431** into the opening; and (c) transmitting aqueous through the device **31**, to bypass the trabecular meshwork **21**, from the deep side to the superficial side of the trabecular meshwork **21**. This "transmitting" of aqueous is preferably passive, i.e., aqueous flows out of the anterior chamber **20** due to a pressure gradient between the anterior chamber **20** and the aqueous venous system **23**.

Another method for increasing aqueous outflow within the eye **10** of a patient, and thus reduce intraocular pressure therein, comprises a) providing at least one bioactive substance incorporated into a trabecular stenting device at about the middle section of the device; b) implanting the trabecular stenting device within a trabecular meshwork of an eye such that the middle section is configured substantially within the trabecular meshwork, the stenting device having a first end positioned in an anterior chamber of the eye while a second end is positioned inside a Schlemm's canal, wherein the first and the second ends of the trabecular stenting device establish a fluid communication between the anterior chamber and the Schlemm's canal; and c) allowing the middle section of the trabecular stenting device to release a quantity of the bioactive substance into the trabecular meshwork. In another embodiment, the at least one bioactive substance or agent is incorporated into the device at about the outlet section for releasing the bioactive agent into Schlemm's canal and/or downstream of Schlemm's canal.

It should be understood that the devices **431** and **31**A are in now way limited to implantation within only Schlemm's canal **20**, as depicted in FIGS. **60** and **61**. Rather, the devices **31** and **431**A may advantageously be implanted within and/or used in conjunction with a variety of other natural outflow pathways, or biological tubular structures, as mentioned above. As will be apparent to those of ordinary skill in the art, the devices **431** and **431**A may advantageously be used in conjunction with substantially any biological tubular structure without detracting from the scope of the invention.

FIG. **64** shows one embodiment of an axisymmetric trabecular stenting device **481** according to the principles of the invention. An axisymmetric device **481** has a coordination of x, r and angle α as shown in FIG. **64**, rather than depending on a conventional coordination of x, y, and z. The device **481** comprises an inlet (proximal) section **482**, an outlet (distal) section **483** and a middle section **484** connecting the inlet section **482** and the outlet section **483**. A lumen **485** of the device **481** is for transporting aqueous, liquid, or therapeutic agents between the inlet section and the outlet section, wherein the therapeutic agent is herein intended to include pharmaceutical agents, drugs, genes, cells, and/or growth factors. The inlet section **482** has at least one inlet opening **486** while the outlet section **483** comprises at least one outlet opening **487**. In some aspect, the outlet section **483** may comprise a plurality of openings **487**, **488** suitably located for outletting axisymmetrically the aqueous, liquid or therapeutic agents, wherein each of the openings **488** is in fluid communication with the lumen **485** of the device **481**.

In one embodiment, at least one bioactive agent is loaded onto the exterior surface or into the pores of the exterior surface of the middle section **404**, **484** of the stenting device **431**, **481** enabling releasing into the trabecular meshwork upon device implantation. In general, the bioactive agents may comprise pharmaceutical agents, drugs, genes, cells, and/or growth factors. In some aspect, at least some bioactive agents may be loaded onto the inner surface or into the pores of the inner surface of the middle section of the stenting devices. In still a further aspect, the middle section **404**, **484** may be constructed of porous material enabling the loaded therapeutic agents controllably releasing to the desired surrounding tissue, wherein the therapeutic agents are diffusible through the pores. Preferably, the middle section **484** has a length (between the inlet section **482** and the outlet section **483**) that is roughly equal to a thickness of the trabecular meshwork **21**, which typically ranges between about 100 μm and about 300 μm.

Some aspects of the invention provide a stent with at least one bioactive agent being loaded onto the exterior surface or into the pores of the exterior surface of the outlet section **409**, **483** of the stenting device **431**, **481** enabling releasing into Schlemm's canal or collector channels upon device implantation.

To further stenting Schlemm's canal after implanting the device **481**, a plurality of elevated (that is, protruding axially) supports or pillars **489** is located at the distal-most end of the outlet section **483** sized and configured for allowing media (for example, aqueous, liquid, balanced salt solution, viscoelastic fluid, therapeutic agents, or the like) to be transported freely. Some aspects of the invention relate to the device **481** having a plurality of elevated (that is, protruding axially) supports or pillars **489** that are made of biodegradable material mixed with at least one bioactive agent. Once implanted, the bioactive agent is slowly released from the biodegradable supports **489** to treat the Schlemm's canal tissue.

In a further aspect, a plurality of the stenting device **481** is loaded in a cartridge to be inserted into a loading chamber of a device delivery applicator **451** or directly loaded inside the loading chamber of a device delivery applicator **451** enabling for multiple stents implantation. In this method, the distal end of the applicator **451** is movably positioned from one location at the trabecular meshwork after implanting a first stent to another location of the trabecular meshwork for implanting a second stent and so forth without withdrawing the applicator out of the anterior chamber of the eye.

Some aspects of the invention provide the device **431**, **481** adapted for a direct release of at least one bioactive agent for treating ocular tissues. As discussed above, the bioactive or therapeutic agents may be compounded within the device **431**, **481** or form a coating on the device **431**, **481**. Any known drug or non-drug therapeutic agents for glaucoma may be utilized, including but not limited to, the following:

U.S. Pat. No. 6,436,703, issued Aug. 20, 2002, the entire contents of which are incorporated herein by reference, discloses a method and compositions comprising novel isolated polypeptides, novel isolated polynucleotides encoding such polypeptides, including recombinant DNA molecules, cloned genes or degenerate variants thereof, especially naturally occurring variants such as allelic variants, antisense polynucleotide molecules, and antibodies that specifically recognize one or more epitopes present on such polypeptides, as well as hybridomas producing such antibodies. The compositions in '703 additionally include vectors, including expression vectors, containing the polynucleotides of the invention, cells genetically engineered to contain such polynucleotides and cells genetically engineered to express such polynucleotides, any of which might be effective in treating trabecular meshwork and/or ocular tissue in general;

U.S. Pat. No. 6,423,682, issued Jul. 23, 2002 and U.S. Pat. No. 6,485,920, issued Nov. 26, 2002, the entire contents of both of which are incorporated herein by reference, disclose the compositions of novel human growth factor antagonist proteins and active variants thereof, isolated polynucleotides encoding such polypeptides, including recombinant DNA molecules, cloned genes or degenerate variants thereof, especially naturally occurring variants such as allelic variants, antisense polynucleotide molecules, and antibodies that specifically recognize one or more epitopes present on such polypeptides, as well as hybridomas producing such antibodies function of mitochondria and toxic substances synthesized as a metabolic byproduct within mitochondria of cells. It is proposed that such compositions with known effects on mitochondrial stability might be effective in treating trabecular meshwork. An antagonistic drug to neutralize the toxic byproduct or a stabilizing drug to effect mitochondrial stability is believed able to restore the mitochondria function and subsequently mitigate the dysfunction of the trabecular meshwork;

U.S. Pat. No. 6,379,882, issued Apr. 30, 2002, the entire contents of which are incorporated herein by reference, discloses a method for reducing cellular damage related to myocardial infarction, glaucoma or another neurodegenerative disease by administering to a subject, a therapeutically effective amount of a test compound as determined by the relative efficacy of the test compound in reducing cell death due to the ischemic condition in an in vitro assay of growth factor or oxygen/glucose and growth factor-deprived retinal ganglion cells. In the present invention, the in vitro cell death of growth factor or oxygen/glucose and growth factor-deprived retinal ganglion cells generally occurs by an apoptotic or necrotic mechanism, wherein the test compound comprises a calcium channel blocker, an N-methyl-D-aspartate, and a bis-benzimidazole;

U.S. Pat. No. 6,489,305, issued Dec. 3, 2002, the entire contents of which are incorporated herein by reference, discloses a method for inhibiting proliferation of ocular fibroblasts or for ameliorating glaucoma surgery failure in a mammal, the method comprising administering to an eye of the mammal during or after glaucoma surgery a p21 cyclin dependent kinase inhibitor, wherein the cyclin dependent kinase inhibitor is administered as a polypeptide or as a nucleotide sequence that encodes the cyclin dependent kinase inhibitor administered in an adenoviral viral vector or administered on a sponge depot;

U.S. Pat. No. 6,455,283, issued Sep. 24, 2002, the entire contents of which are incorporated herein by reference, discloses a method of vascular endothelial growth factor-E (VEGF-E). VEGF-E is a novel polypeptide related to vascular endothelial growth factor (VEGF) and bone morphogenetic protein 1. VEGF-E has homology to VEGF including conservation of the amino acids required for activity of VEGF. VEGF-E can be useful in wound repair, as well as in the generation and regeneration of tissue. It is proposed that such VEGF, VEGF-E and their respective antagonists with known effects on tissue regeneration or anti-regeneration might be effective in treating trabecular meshwork or ocular tissue in general;

U.S. Pat. No. 6,476,211, issued Nov. 5, 2002, the entire contents of which are incorporated herein by reference, discloses human CD39-like protein polynucleotides isolated from cDNA libraries of human fetal liver-spleen and macrophage as well as polypeptides encoded by these polynucleotides and mutants or variants thereof. CD39 (cluster of differentiation 39) is a cell-surface molecule recognized by a "cluster" of monoclonal antibodies that can be used to identify the lineage or stage of differentiation of lymphocytes and thus to distinguish one class of lymphocytes from another. It is proposed that such CD39 polynucleotides with known effects on antibody specifics might be effective in treating trabecular meshwork or ocular tissue in general;

U.S. Pat. No. 5,780,052, issued Jul. 14, 1998, the entire contents of which are incorporated herein by reference, discloses a method of salvaging a target cell from cell death, comprising contacting a target cell having a disrupted cell membrane with a specific affinity reagent-liposome conjugate in an amount effective and for a time sufficient to allow the conjugate to prevent cell death due to membrane disruption. The patent discloses methods of delivering a selected agent into a damaged target cell for diagnosis and therapy, wherein the conjugate comprises a biological agent selected from the group consisting of fibroblastic growth factor-β, angiogenic factors, high energy substrates for the myocardium, antioxidants, cytokines and contrast agents, which might be effective in treating trabecular meshwork or ocular tissue in general;

U.S. Pat. No. 6,475,724, issued Nov. 5, 2002, the entire contents of which are incorporated herein by reference, discloses a method of treating glaucoma which comprises administering to a glaucomatous patient an effective amount of an agent that inhibits the synthesis if a TIGR (trabecular meshwork inducible glucocorticoid response) protein or gene, which might be effective in treating trabecular meshwork or ocular tissue in general;

U.S. Pat. No. 6,475,784, issued Nov. 5, 2002, the entire contents of which are incorporated herein by reference, discloses a method for polypeptides having anti-angiogenic activity and nucleic acids that encode these polypeptides. The anti-angiogenic polypeptides include at least kringles 1-3 of plasminogen. The patent '784 also provides methods of using the polypeptides and nucleic acids for inhibiting angiogenesis and other conditions characterized by undesirable endothelial cell proliferation. Angiostatin, which is an angiogenesis inhibitor, is a naturally occurring internal cleavage product of plasminogen, wherein human plasminogen has five characteristic protein domains called "kringle structures." It is proposed that such angiostatin with known effects on inhibiting angiogenesis might be effective in treating trabecular meshwork and/or ocular tissue in general;

U.S. Pat. No. 6,436,703, issued Aug. 20, 2002, the entire contents of which are incorporated herein by reference, discloses a method and compositions comprising novel isolated polypeptides, novel isolated polynucleotides encoding such polypeptides, including recombinant DNA molecules, cloned genes or degenerate variants thereof, especially naturally occurring variants such as allelic variants, antisense polynucleotide molecules, and antibodies that specifically recog-

nize one or more epitopes present on such polypeptides, as well as hybridomas producing such antibodies. The compositions in '703 additionally include vectors, including expression vectors, containing the polynucleotides of the invention, cells genetically engineered to contain such polynucleotides and cells genetically engineered to express such polynucleotides, any of which might be effective in treating trabecular meshwork and/or ocular tissue in general;

U.S. Pat. No. 6,451,764, issued Sep. 17, 2002, the entire contents of which are incorporated herein by reference, discloses a method of treating vascular tissue and promoting angiogenesis in a mammal comprising administering to the mammal an effective amount of the composition comprising VRP (vascular endothelial growth factor-related protein). The disclosure '764 further provides a method for treating trauma affecting the vascular endothelium comprising administering to a mammal suffering from the trauma an effective amount of the composition containing the VRP, or a method for treating a dysfunctional state characterized by lack of activation or lack of inhibition of a receptor for VRP in a mammal. It is proposed that such angiogenesis promoter and its antagonists with known effects on promoting or inhibiting angiogenesis might be effective in treating trabecular meshwork and/or ocular tissue in general; and

U.S. Pat. No. 5,986,168, issued Nov. 16, 1999, the entire contents of which are incorporated herein by reference, discloses a prosthesis artificially made in vitro and comprising a time dependent immobilized and insoluble bioabsorbable substance shaped into a prosthetic shape for implantation into a mammal, and having physical means for immobilizing and insolubilizing of the bioabsorbable substance for a predetermined period of time after implantation, wherein the prosthesis may comprise fibroblast growth factors, which fibroblast growth factors or their antagonists might be effective in treating trabecular meshwork and/or ocular tissue in general.

Scar-Retarding (Antifibrotic) Substances and Background

It was reported that Monoclonal antibodies are a promising modality for prevention of scarring after trabeculectomy, according to a current research (OCULAR SURGERY NEWS Sep. 19, 2002 entitled *TGF-beta may help prevent postop scarring*). Several studies are investigating the interaction between growth factors and their role in the induction of postoperative scarring of the filtering bleb. Wimmer and colleagues note in the September issue of *Der Ophthalmologe* that among the growth factors being studied in several trials, TGF-beta 2 plays a key regulatory function. Its concentration in the aqueous humor of patients with primary open-angle glaucoma is significantly elevated, and both in vivo and in vitro studies have shown the growth factor to demonstrate "promising inhibition of scarring after subconjunctival application." In addition, current research indicates the growth factor is a safe and well-tolerated approach to managing postop scarring. It is one aspect of the present invention to provide a growth factor (TGF-beta 2 and the like) to trabecular meshwork at an effective amount to mitigate, eliminate, or retard scar formation at or around the trabecular meshwork. It is a further aspect of the present invention to provide a method of direct delivery of at least one growth factor (TGF-beta, including TGF-beta 2, analog, derivatives and the like) to trabecular meshwork at an effective amount to mitigate, eliminate, or retard scar formation at or around the trabecular meshwork to ocular tissue through an ocularly inserted apparatus or an implant, including a "fistula." In one aspect, the bioactive agent of the invention comprises a scar retarding substance.

U.S. Pat. No. 5,324,508, issued Jun. 28, 1994, the entire contents of which are incorporated herein by reference, discloses a macrophage monokine product having a molecular weight of no more than about 10,000 Dalton, wherein the macrophage monokine appears to be generally effective in inhibiting scar tissue. It is one object of the present invention to incorporate the macrophage monokine product onto a trabecular stent for scar management.

Prof. Peng Khaw (of the Institute of Ophthalmology and Moorfields Eye Hospital) discloses that injecting a neutralizing antibody to the protein transforming growth factor beta$_2$ (TGF-b$_2$) after glaucoma surgery reduced the scarring that is the primary cause for poor postoperative IOP control in a pilot clinical study conducted at Moorfields Eye Hospital and the Western Eye Hospital. Scarring after surgery is the main cause of treatment failures, but the attempt to diminish scarring with anti-cancer drugs can lead to its own set of problems.

Anti-cancer drugs used with glaucoma surgery, which to date have included 5-fluorouracil (5FU) and mitomycin-C, can lead to the creation of acellular, thin, cystic drainage blebs that may leak, resulting in hypotony and potentially blinding infections. Anti-cancer drugs work by killing cells, so they have a lot of potential side effects. Therefore, they are not the ideal treatment, particularly if you want to optimize the pressure lowering in every patient having surgery.

Scarring processes are a big problem in the eye and surrounding structures. Scarring plays a part in either the primary disease or treatment failure of most blinding conditions in the world today. An exception to this repair response is found in the fetal stage, when scarring is minimal. Instead, regeneration primarily occurs. This is associated with low levels of TGF-b in the womb.

It is therefore one aspect of the present invention to provide a method of maintaining a fistula in trabecular meshwork with a scar-retarding substance for re-establishing physiologic outflow in the eye. In one embodiment, the fistula is biodegradable.

U.S. Pat. No. 5,922,369, entire contents of which are incorporated herein by reference, discloses a method of treating eye conditions with human leukocyte elastase (HLE) inhibitory agents. More specifically, it is one object of the present invention to provide a method of reducing tissue or corneal scarring comprising delivery of human leukocyte elastase inhibitory agents an effective amount for scar reducing of a free or polymer-bound HLE inhibitory agent to ocular tissue through an ocularly inserted apparatus or an implant, including a fistula.

FIG. **65** shows one embodiment for a fistula without a lumen for transporting aqueous. The fistula may be made of a soft flexible material with special surface characteristics to facilitate aqueous transporting along its surface. The material may be selected from a group consisting of silicone, polyurethane, acrylics, and the like. The special surface characteristics for facilitating aqueous transportation may include hydrophilicity, hydrophobicity, surface charge, heparinized surface, surface pH, and drug-coated surface. The surface characteristics may also include mechanical or physical properties such as surface elasticity, surface configuration, shape memory and the like. FIG. **65** shows a fistula **466** comprising a proximal terminal means **467** sized and shaped to be received within the anterior chamber **20** and a distal terminal means **468** sized and shaped to be received within Schlemm's canal **22**. A majority of the surface **469** with special characteristics contacts the trabecular meshwork **21** where the facilitated aqueous transportation takes places. The cross-sectional configuration may be any shape, including circular, oval, star, random, and arbitrary or the like.

Some aspects of the invention provides a trabecular bypass stent that is implantable within an eye, the device comprising: an inlet section having an inlet end exposed to an anterior chamber; an outlet section having an outlet end exposed to Schlemm's canal, wherein the device is configured to permit fluid entering the inlet end and then exiting the outlet end; and at least one bioactive agent is loaded onto the stent, wherein the bioactive agent is selected from a group consisting of TGF-beta, a gene, a growth factor, a scar-retarding (or scar-mitigating, scar-limiting, scar-inhibiting) substance. In one aspect of the invention, the therapy combines at least one bioactive agent loaded onto a trabecular bypass stent and a topically administered IOP-lowering eye drop medicine selected from a group consisting (1) Miotics (e.g., pilocarpine, carbachol, and acetylcholinesterase inhibitors), (2) Sympathomimetics (e.g., epinephrine and dipivalylepinephxine), (3) Beta-blockers (e.g., betaxolol, levobunolol and timolol), (4) Carbonic anhydrase inhibitors (e.g., acetazolamide, methazolamide and ethoxzolamide), and (5) Prostaglandins (e.g., metabolite derivatives of arachidonic acid).

Although preferred embodiments of the invention have been described in detail, including devices loaded with TGF-beta and/or bioactive agents, certain variations and modifications will be apparent to those skilled in the art, including embodiments that do not provide all of the features and benefits described herein. Accordingly, the scope of the present invention is not to be limited by the illustrations or the foregoing descriptions thereof, but rather solely by reference to the appended claims and their equivalents.

What is claimed is:

1. A method of treating an ocular disorder, comprising:

introducing an implant into an anterior chamber of an eye;

implanting the implant into eye tissue adjacent the anterior chamber such that a proximal end of the implant resides in the anterior chamber following implantation;

eluting a therapeutic agent from the implant into the eye; and

controlling release of the therapeutic agent from the implant,

wherein introducing an implant comprises introducing the implant into the anterior chamber such that at least a distal end of the implant is temporarily in the anterior chamber.

2. The method of claim **1**, wherein controlling release comprises controlling release of the therapeutic agent at a chosen rate.

3. The method of claim **2**, wherein the chosen rate is episodic or periodic.

4. The method of claim **1**, wherein controlling release comprises controlling release of the therapeutic agent for a selected duration.

5. The method of claim **4**, wherein the selected duration is episodic or periodic.

6. The method of claim **1**, wherein controlling release comprises controlling release of the therapeutic agent at a chosen rate and for a selected duration.

7. The method of claim **6**, wherein the chosen rate and/or the selected duration are episodic or periodic.

8. The method of claim **1**, wherein eluting a therapeutic agent from the implant comprises eluting the therapeutic agent into at least one of the anterior chamber, a physiologic outflow pathway of the eye, and a space adjacent a choroid of the eye.

9. The method of claim **1**, wherein the therapeutic agent comprises an antiproliferative agent or an anti-inflammatory drug.

10. The method of claim **1**, wherein the therapeutic agent comprises a compound for treating glaucoma or ocular hypertension.

11. The method of claim **1**, wherein the therapeutic agent is contained within the implant.

12. The method of claim **1**, wherein the therapeutic agent is coated on the implant.

13. The method of claim **1**, wherein introducing an implant into an anterior chamber of an eye involves forming an incision in corneal tissue.

14. The method of claim **1**, wherein introducing an implant into an anterior chamber of an eye involves forming an incision proximate a limbus of the eye.

15. The method of claim **1**, wherein introducing an implant into an anterior chamber of an eye involves forming a self sealing incision.

16. The method of claim **1**, wherein implanting the implant involves placing the implant in contact with a choroid of the eye.

17. The method of claim **1**, wherein the implant comprises at least one anchor.

* * * * *